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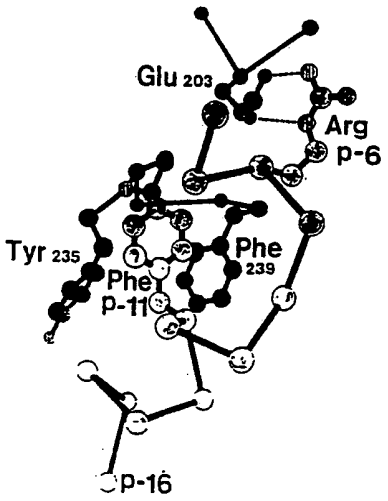
(54) Title: METHODS OF DESIGNING SPECIFIC AFFECTORS USING THREE-DIMENSIONAL CONFORMATION OF ENZYME/AFFECTOR COMPLEX

(57) Abstract

The present invention includes methods for rational drug design. One exemplary method disclosed herein teaches the preparation of a highly specific affector of a first enzyme when the first enzyme is a member of a class of enzymes having a conserved catalytic core with a plurality of invariant residues. This method comprises identifying a second enzyme that is a member of that class of enzymes and has a known affector. The affector can be an inhibitor or activator of the second enzyme. In the practise of the method, a first complex is formed between the second enzyme and the known affector and data is obtained regarding the three-dimensional coordinates of the invariant residues in the complex. These coordinates are used to form a template. A model is then generated in which the first enzyme is in a conformation with the invariant residues in substantially the same conformation as in the template. Changes in the variable residues of the catalytic core of the first enzyme are compared to the variable residues in the catalytic core of the second enzyme. The second enzyme is modified to include these non-conserved changes and an affector is designed using computer modelling that will induce a conformation on the catalytic core of the first enzyme in which the invariant residues are in substantially the same coordinates as the coordinates of the template when the first enzyme is formed as a second complex with the newly designed affector. The designed affector can be further refined to provide improved affector activity.



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METHODS OF DESIGNING SPECIFIC AFFECTORS USING THREE DIMENSIONAL CONFORMATION OF ENZYME/AFFECTOR COMPLEX

Field of the Invention

The present invention relates to rational design of specific affectors for a given enzyme using data obtained regarding the three dimensional conformation of an enzyme/affector complex. More particularly, it relates to such methods wherein the conformation of the conserved catalytic core of a given enzyme class is elucidated and highly specific affector molecules for a particular member of that class are designed.

Background of the Invention

Drug design based on an analysis of the structural features of a molecule is still in its infancy. At present, an analysis of X-ray crystallographic data at best permits the design of broadly acting affector molecules. While these affector molecules can be further refined to impart some selectivity, affector design does not produce molecules having the fine tuned specificity of, for example, an antibody for its antigen. This level of selectivity control is not always necessary; however, therapeutic regimes directed to the control of enzymes involved in certain cancers, genetic disorders, and infectious agents will require this type of selectivity.

Enzymes can be classified into broad families or classes having similar activities, with each enzyme having a specific function. For example, many proteins phosphorylate their substrate. These enzymes are broadly labelled as kinases. A myriad of kinases exist for a myriad of functions. Within this broad group, kinases can be subgrouped based on similarities in substrate, requirements for additional cofactors or similar amino acid residues that are targets for phosphorylation.

Within any given cell, there may be many active members of a given enzyme family. If one member of the family shows aberrant activity, then it may be therapeutically advantageous to alter the activity of this single enzyme to the exclusion of other similar or related enzymes. Such is the case for the protein kinase family where aberrant phosphorylation events can be associated with abnormal cell growth and regulation. This is observed in proto-oncogene related cancers. For example, the $pp60^{c\text{-}src}$ protein, needs to be controlled to the exclusion of other protein kinases in order to maintain normal cell metabolism.

Protein phosphorylation as a mechanism for regulating protein activity was first recognized in 1955 with glycogen phosphorylase. Protein phosphorylation and dephosphorylation is widespread and impacts nearly all aspects of growth and homeostasis

in the eukaryotic cell. Protein kinases catalyze the transfer of the γ-phosphate of MgATP to a protein substrate. The protein kinases, constitute a large and very diverse family of enzymes. Although these enzymes differ in size, substrate specificity, mechanism of activation, subunit composition, and subcellular localization, all, nevertheless, share a homologous catalytic core that has been conserved throughout evolution.

It is not yet possible to regulate a given enzyme at will. While there are hundreds of different protein kinases, only a few of these can be readily purified. Moreover, even among those enzymes that can be purified, many cannot be used for X-ray crystallographic studies. The sequences of many enzymes have been cloned and expressed; however, not all of these are chemically active. Therefore, even if a molecule that cannot be readily purified is cloned and expressed, it may not be functional and thus, would not provide an adequate model for structural studies. Further, even if a recombinant protein is functional, it may not be readily crystallizable. These and other roadblocks have heretofore prevented the design or identification of affector molecules directed to a particular enzyme. Thus, heretofore it has not been possible to provide a method for the design of affector molecules for a given member of an enzyme family.

Brief Description of the Figures

Figure 1 illustrates the general topological arrangement of the catalytic subunits from a number of different protein kinases.

Figure 2 diagrams the placement of the catalytic region within various members of the protein kinase family.

Figure 3 is a stereo view of the electron density for the structure determination. Figure 3A provides the density calculated to 2.7 Å. Figure 3B provides the density calculated with 10.0 to 2.7 Å refined model phases.

Figure 4 is a stereo view of the C-α backbone and includes twenty residues of PKI(5-24).

Figure 5 provides data on the location and orientation of MgATP. Figure 5A illustrates the general localization of MgATP. Figure 5B is a close-up of difference density enclosing an oriented model of AMP.

Figure 6 is an overall two dimensional topology diagram for the C-subunit. of cAPK.

Figure 7 provides stereo views of selected conserved areas.

Figure 8 illustrates the conserved catalytic core of c-AMP dependent protein kinase. Figure 8A is a space-filling model of the catalytic core. Figure 8B is a diagram of the

conserved catalytic core using the RIBBON program of the PAP package. Figure 8C is a space-filling model identical to A, but includes PKI(5-24).

Figure 9 diagrams the conformation of bound PKI (5-24).

Figure 10 illustrates the high affinity binding site interactions between the catalytic subunit and the inhibitor peptide. In Figure 10A the P-11 Phe ring (numbered 356) is shown in relation to three nearby hydrophobic residues of the C-subunit. Figure 10B illustrates the interactions of the P-11 Phe and P-6 Arg sidechains with the C-subunit.

Figure 11 summarizes the interactions that contribute to recognition of the common consensus region of the inhibitor peptide.

Figure 12 illustrates the consensus recognition site binding interactions. Figure 12A is an illustration of the electron density corresponding to the anionic P-3 site. Figure 12B illustrates the electron density of the P-2 Arg side chain. Figure 12C illustrates the electron density of the P+1 Ile sidechain.

Figure 13 illustrates the catalytic site area. Figure 13A provides the site of catalysis together with the probable catalytic base sidechain of Asp 166 near the β-C of the P Ala. Figure 13B diagrams the consensus recognition site residues Arg-Arg-Asn-Ala-Ile. Figure 13C shows the phosphate of Thr 197 buried among sidechains of cationic and H-bonding residues.

Figure 14 is a schematic illustrating the relationship of invariant amino acids at the active site.

Figure 15 is a schematic of the conserved and variable regions of the catalytic subunit.

Figure 16 illustrates the amino acids present in PKI(5-24) that provide important interactions with cAPK.

Figure 17 provides a list of the coordinates that define the three-dimensional template.

Figure 18 provides photographs of the crystal forms.

Summary of the Invention

In accordance with one aspect of the present invention, there is provided a method of designing a highly specific affector which exerts an effect on the activity of a first enzyme. In this method, the first enzyme is a member of a class of enzymes having a conserved catalytic core. The method comprises the following steps: identifying a second enzyme that is a member of the class in which a first affector can affect the activity of the second enzyme, forming a first complex of the first affector and the second enzyme, obtaining data

regarding the conformation of the second enzyme at sites greater than 5 Å from the site of catalysis of the second enzyme in the first complex, and designing an affector which induces a conformation on the first enzyme at sites greater than 5 Å from the site of catalysis thereof which is homologous to the conformation of the second enzyme at homologous sites in the first complex, when the affector is formed as a second complex with the first enzyme. Preferably, this method additionally comprises crystallizing the first complex and obtaining X-ray crystallography data therefrom. In a preferred form of this method, all of the members of the class have related functions, and the catalytic cores of all of the members of the class have conserved amino acid residues. In this form of the method, preferably the designing step comprises designing an affector having homologous topography and charge fields that complement the catalytic core of the first enzyme and capable of inducing a conformation wherein the conserved amino acid residues of the first enzyme are in homologous locations to the second enzyme in the first complex. The affectors can be inhibitors, activators or other affectors of enzyme activity. The first affector can be all or a portion of the first enzyme, and the first complex can be a holoenzyme. The class of enzymes can comprise protein kinases or any other suitable class. The second enzyme can be a viral oncogene product or a cellular homologue thereof, such as p60 v-Src from RSV or its cellular homologue, pp60 c-src. The second enzyme can also be cAMP-dependent protein kinase. The second enzyme can be a native mammalian protein kinase or a recombinant protein kinase. In a preferred form of the method, the designing step comprises identifying a potential affector likely to induce a conformation on the catalytic core of the first enzyme which is homologous to the conformation of the catalytic core of the second enzyme in the first complex, when the affector is formed as a second complex with the first enzyme, and determining whether the potential affector induces the conformation through the use of a technique selected from the group consisting of computer modelling, small angle neutron scattering, and circular dichroism. In this preferred method, the potential affector comprises a peptide, and the potential affector comprises a molecule selected from the group consisting of nucleotides, polynucleotides, alcohols, polymers, lipids carbohydrates, sugars, native or synthetic molecules, protein and organic compounds and combinations thereof. In accordance with this aspect of the invention, the method can include producing the affector. Thus, the present invention also includes the affector produced from the method.

In another aspect of the present invention, there is provided another method of designing a highly specific affector which exerts an effect on the activity of a first enzyme.

In this method, the first enzyme is also a member of a class of enzymes having conserved residues at an affector binding site. This method comprises the following steps: identifying a second enzyme that is a member of the class in which a first affector can affect the activity of the second enzyme, the first affector having a dissociation constant with the second enzyme of less than 1 μM, forming a first complex of the first affector and the second enzyme, obtaining data regarding the conformation of the affector binding site of the second enzyme in the first complex, and designing an affector which induces a conformation on the affector binding site of the first enzyme which is homologous to the conformation of the affector binding site of the second enzyme in the first complex, when the affector is formed as a second complex with the first enzyme. In one form of this method, the class of enzymes has a nucleotide binding site and each of the affectors is capable of binding to the nucleotide binding site.

In still another aspect of the present invention, there is provided another method of designing a highly specific affector which exerts an effect on the activity of a first enzyme. In this method, the first enzyme is also a member of a class of enzymes having a conserved catalytic core. This method comprises the following steps: identifying a second enzyme that is a member of the class in which a first affector can affect the activity of the second enzyme, forming a first complex of the first affector and the second enzyme, the first complex having at least three points of contact between the first affector and second enzyme, obtaining data regarding the conformation of the catalytic core of the second enzyme in the first complex, and designing an affector which induces a conformation on the catalytic core of the first enzyme which is homologous to the conformation of the catalytic core of the second enzyme in the first complex, when the affector is formed as a second complex with the first enzyme.

Still another aspect of the present invention provides a crystallized protein kinase/affector complex having stable decay characteristics over 15 minutes and a crystallized protein kinase/affector complex having a Bragg spacing diffraction limit of less than 4Å. Preferably, the crystallized protein kinase of this aspect of the invention exhibits both of these characteristics. The present invention also provides a crystallized complex of a cAMP-dependent protein kinase and an inhibitor thereof. This crystallized complex can be used in an X-ray crystallography procedure to produce data regarding the three dimensional structure of the cAMP-dependent protein kinase in the complex, and this data can be used for designing an inhibitor of a second protein kinase which will induce a similar three dimensional structure on the active site of the second protein kinase as the three

dimensional structure of the cAMP-dependent protein kinase in the complex. Thus, the present invention also includes an inhibitor designed by this method.

Another preferred method of the present invention involves preparing a highly specific affector of a first enzyme, with the first enzyme being a member of a class of enzymes having a conserved catalytic core with a plurality of invariant residues. This method comprises the following steps: identifying a second enzyme that is a member of the class and having a known affector thereof, forming a first complex of the second enzyme and the known affector, obtaining data regarding the three dimensional coordinates of the invariant residues in the first complex, the coordinates forming a template, generating a model wherein the first enzyme is in a conformation in which the invariant residues are in substantially the same conformation as in the template, identifying a change in the variable residues in the catalytic core of the first enzyme in the conformation of the template when compared to the variable residues in the catalytic core of the second enzyme in the conformation of the template, preparing a modified form of the second enzyme, wherein the modified second enzyme includes a non-conserved change identified through this method, and designing an affector which computer modelling indicates will induce a conformation on the catalytic core of the first enzyme in which the invariant residues are in substantially the same coordinates as the coordinates of the template, when the first enzyme is formed as a second complex with the affector designed in this step. Preferably the identified change is a non-conserved change in the variable residues. In a preferred form of this method, the method also includes forming a third complex of the modified second enzyme and an affector capable of binding thereto, obtaining data regarding the three dimensional coordinates of the invariant residues in the third complex, and using the data obtained in the previous step to design an affector which computer modelling indicates will induce a conformation on the catalytic core of the first enzyme in which the invariant residues are closer to the coordinates of the template than the conformation induced by the affector designed previously, when the first enzyme is formed as a fourth complex with the affector designed in this step. The affector used for computer modelling can be the known affector. Preferably, the method also includes modifying the computer modelling in light of the data obtained through the method prior to designing the affector. Amino acid sequence data relating to the catalytic cores of the first and second enzymes is preferably obtained. Site directed mutagenesis of a recombinantly produced second enzyme can be used in accordance with the method. In one preferred aspect of this method, the coordinates of the template are substantially as shown in Figure 17 and the template can include

coordinates separated by the distances substantially as shown in Table 4. The affectors can be inhibitors or other affectors. The method can also include preparing the designed affector. Thus, the present invention also includes the affectors prepared through this method, and also includes pharmaceutical compositions containing these affectors.

The present invention also includes a method of designing a specific inhibitor for a protein kinase, comprising the following steps: obtaining data regarding the three-dimensional structure of a first protein kinase, and using the data in the design of an inhibitor for a second, different, protein kinase. The first protein kinase is preferably cAMP dependent protein kinase or an analogue thereof. The obtaining step preferably comprises crystallizing a complex of cAMP dependent protein kinase and an inhibitor thereof, and additionally includes obtaining X-ray crystallography data on the crystallized complex obtained from the crystallizing step. Thus, information regarding the structure of the crystallized complex obtained in the crystallizing step through circular dichroism, small angle neutron scattering, or other chemical procedures can be obtained.

In a preferred form of the present invention, there is provided the use of the data of Figure 17 or of Table 4 in the design of an affector for a protein kinase.

Still another aspect of the present invention involves a method of preparing a highly specific inhibitor of a first enzyme. The first enzyme is a member of a class of enzymes having a conserved catalytic core with a plurality of invariant residues. This method includes the following steps: (a) identifying a second enzyme that is a member of the class and having a known first inhibitor thereof, (b) forming a first complex of the second enzyme and the first inhibitor, (c) obtaining data regarding the three dimensional coordinates of the invariant residues in the first complex, (d) designing a second inhibitor which computer modelling indicates will induce a conformation on the catalytic core of the first enzyme in which the invariant residues are in substantially the same coordinates as the coordinates obtained in step (c), when the first enzyme is formed as a second complex with the second inhibitor, (e) preparing the second inhibitor, (f) forming a third complex of the second inhibitor and a third enzyme complexable therewith, the third enzyme having a plurality of the invariant residues, (g) obtaining data regarding the three dimensional coordinates of the invariant residues in the third complex, and (h) using the data obtained from step (g) to design a third inhibitor which computer modelling indicates will induce a conformation on the catalytic core of the first enzyme closer to that in which the invariant residues are in substantially the same coordinates as the coordinates obtained in step (c) than induced by the second inhibitor, when the first enzyme is formed as a fourth complex with the third

inhibitor. This first inhibitor is in one embodiment of this method an inhibitory domain of the second enzyme. The third enzyme preferably contains at least 5 invariant residues, and can be a naturally occurring enzyme or a mutant enzyme.

Still another aspect of the present invention involves a method of determining the efficacy of a first affector in affecting a first enzyme that is a member of a class of enzymes having a plurality of invariant residues among the members of the class. This method includes the following steps: determining the three dimensional coordinates of the invariant residues of a second enzyme in a first conformation wherein the second enzyme is in a complex with a second affector that is a strong affector of the enzyme, determining the three dimensional coordinates of the invariant residues of the second enzyme in a second conformation wherein the enzyme is in a conformation other than the first conformation, identifying the mobile invariant residues of the enzyme, the mobile invariant residues being those invariant residues at coordinates substantially different in the first conformation than in the second conformation, determining the three dimensional coordinates of the mobile invariant residues of the first enzyme when the first enzyme is in a conformation wherein the first enzyme is in a complex with the first affector, comparing the three dimensional coordinates of the mobile invariant residues of the first enzyme in the conformation with the coordinates of the mobile invariant residues of the enzyme in the first conformation, wherein relatively small differences in the coordinates indicate relatively high efficacy of the first affector. The step of determining the coordinates of the first enzyme in the conformation is preferably performed using computer modelling of the conformation. The steps of determining the first and second conformations preferably comprise obtaining X-ray crystallographic data of the enzyme. The second conformation can be a conformation produced by a ternary complex, such as one comprising a protein kinase, a nucleotide and an affector. The second conformation can also be a conformation produced by the second enzyme not complexed with a ligand, or the same enzyme as the first enzyme.

In an additional aspect of the present invention, there is provided a method of designing specific inhibitors of a first protein kinase having a template defined by a plurality of invariant residues present in substantially all protein kinases. This method comprises the following steps: obtaining data regarding the three dimensional coordinates of the invariant residues of a second protein kinase and of the points of contact between the second protein kinase and a known inhibitor thereof, the coordinates being obtained when the second protein kinase is formed as a complex with the known inhibitor, generating a model of the first protein complex wherein the template is defined by the positions of the invariant

residues in the complex, examining the amino acid residues present in the first protein kinase at positions corresponding to the points of contact in the complex, and designing an inhibitor of the first protein kinase capable of forming ionic and hydrophobic interactions with the amino acid residues. The method of Claim 62, wherein the second protein kinase is cAMP dependent protein kinase. The known inhibitor can be PKI(5-24). For this known inhibitor, the points of contact in the complex preferably comprise positions corresponding to the positions selected from the group consisting of P+1, P-2, P-3, P-6 and P-11 along the known inhibitor. The positions corresponding to the points of contact in the examining step preferably comprise positions within a sphere having a radius of 11 Å, more preferably 6 Å, from the coordinates of the point of contact obtained in the obtaining step. The designing step preferably additionally comprises designing the inhibitor to form appropriate hydrogen bonding with the amino acid residues.

Further details concerning the present invention are provided in the following detailed description.

Detailed Description of the Invention

CITED REFERENCES INCORPORATED BY REFERENCE

A number of articles are specifically cited herein as providing background information useful, but not essential, to those of ordinary skill in the art in the practice of the present invention. As such, the disclosure of each of these articles is hereby explicitly incorporated by reference.

INTRODUCTION

The protein kinase family of enzymes is used as a model for this invention. These enzymes are involved at all levels of regulation in the eukaryotic cell. They act as "transistors" for the cell, receiving signals and amplifying the message inside the cell. Protein kinases receive hormone signals from outside the cell. They are involved in cell growth, for cellular homeostasis, and for triggering the steps of mitosis.

In addition, many oncogenes code for protein kinases. These oncogenic protein kinases are also very diverse in their structure and location within the cell. However, all are derived from normal cellular components and all, in one way or another are defective in their ability to be turned off. In other words, they are constitutively active in contrast to their protooncogene counterparts which are turned off in the absence of the appropriate signal. Thus, protein kinases are not only an essential part of normal cell growth and division, but, can lead to oncogenesis when their normal function becomes genetically impaired.

Diversity is a hallmark of the protein kinase family. For example, growth factor receptors, such as the insulin receptor, are large proteins with a major extracellular domain for binding growth factor, a single membrane spanning domain, and an intracellular protein kinase domain that is activated in response to growth factor binding. The kinase activity is limited to a specific domain of the protein. Control of the insulin receptor may play an important role in the control of diabetes. Protein kinase C is activated by diacyl glycerol and Ca^{2+} and is also activated by the tumor promoting phorbol esters. It is a cytoplasmic protein that in its active state is associated with the plasma membrane. Another protein kinase, cdc2, associates with cyclin B and is an essential trigger for mitosis. The transforming protein in Rous Sarcoma Virus, $pp60^{v\text{-}src}$ is anchored to the cytoplasm surface of membranes. In spite of the diversity in size, subunit composition, location in the cell, and mechanism of activation, all protein kinases share a common enzymatic activity and a conserved catalytic core, indicating that all have likely evolved from a common functional precursor. Thus, one aspect of the present invention provides a method for developing highly selective inhibitors for members of the protein kinase family.

The first protein kinase to be purified was phosphorylase kinase. The second was phosphorylase kinase kinase, later renamed cAMP-dependent protein kinase (EC2.7.1.37:ATP:protein serine phosphotransferase) when its broader substrate specificity was appreciated. Not only was cAMP-dependent protein kinase (cAPK) one of the first protein kinases to be characterized, it also is one of the simplest and best understood biochemically. Its simplicity is due primarily to its mechanism of activation, which involves subunit dissociation. With the exception of the oncogenic enzymes, all protein kinases typically are maintained in an inactive state in the absence of the appropriate activating signal. In the case of cAPK, the ligand triggering activation is cAMP, one of the first recognized second messengers for hormone signalling. In the absence of cAMP, the enzyme is sequestered as an inactive holoenzyme containing two regulatory (R) and two catalytic (C) subunits. When intracellular cAMP levels are elevated, the cyclic nucleotide binds to the R-subunit, thus causing the complex to dissociate into a R_2 dimer and two free and active C-subunits. The general consensus sequence recognized by the C-subunit is Arg-Arg-X-Ser/Thr-Y, where X is any small residue and Y is a large hydrophobic group. The conserved catalytic core found in all protein kinases is contained within this relatively simple monomeric C-subunit.

This invention provides the first crystal structure of a protein kinase with its catalytic subunit intact. Knowledge of the conformation of the catalytic structure of cAPK is central

to the understanding of protein kinase activity. Not only is the structure of the cAMP-dependent protein kinase catalytic site provided, but, the crystals contain a bound inhibitor peptide. This inhibitor peptide, PKI(5-24), is a fragment of the heat stable protein kinase inhibitor (PKI). This peptide includes the consensus features common to all peptide substrates and inhibitors of cAMP-dependent protein kinase. In addition, it contains other features that convey unique high affinity binding characteristics. Thus, precise properties of binding and interaction are described. From this data, a template is derived from which all other protein kinases can be modelled and from which other inhibitors can be designed.

One of the more important questions regarding protein phosphorylation is how the targeted protein substrate is recognized by a specific protein kinase. This question has remained particularly elusive until now because the determinants for peptide recognition are widely dispersed and in some cases well-removed from the actual site of phosphotransfer. Owing to its simplicity as well as its relative ease of purification, the catalytic or C-subunit of cAMP-dependent protein kinase serves here as a prototype for identifying functional sites that are involved in substrate recognition and catalysis. Chemical analyses and procedures, such as affinity labeling, group specific labeling, and fluorescence energy transfer all have provided clues about regions involved in peptide recognition, MgATP binding, and catalysis. Substrate analogues provide indirect information about binding sites important for affector molecule specificity. Further NMR, circular dichroism, small angle neutron scattering (SANS) and other chemical procedures offer further insight into the structure of the enzyme. However, X-ray crystallography provides a comprehensive three dimensional structure that can confirm and integrate these other techniques.

The expression of the C-subunit in E. coli not only facilitated these structural studies, but also has permitted recombinant approaches to be used to further modify the active site of cAPK and thereby mimic the reactive site of other protein kinases. Information to aid in these studies is obtained from sequence data available for the protein kinase family. Hanks et al., Science 241: 42, 1988, is one source of such data. Such sequence comparisons have identified highly conserved regions including several invariant residues, variable regions, and places where inserts and deletions can be tolerated. Both chemical and sequence information are used here to verify the structure data obtained from the X-ray diffraction studies. As will be disclosed herein, this body of information permits the design of other affector molecules specific for other protein kinases. Further, this information serves as guidelines for the design of specific affector molecules for enzymes from a wide variety of enzyme families.

The existing basis for the design of specific inhibitors for protein kinases, in the absence of the three dimensional structure provided herein, relies on the use of synthetic peptides based primarily on the sequences of known substrates and inhibitors. In the case of cAMP-dependent protein kinase, there are some very specific high affinity peptides available. Existing inhibitors also include nucleotide and nucleoside derived compounds found through traditional means. However, these nucleoside and nucleotide inhibitors do not generally exhibit the type of specificity observed with peptide inhibitors. In general, such specific peptide inhibitors are not available for other protein kinases. Specificity for cAMP-dependent kinase improves with the addition of amino acids postulated to lie outside of the catalytic core. We have discovered that these regions are also important for inhibitor design. Knowledge of these sites provides a "lock" to permit for the first time the tailoring of inhibitors for any given protein kinase. Thus, one important aspect of the invention lies in the design of the "lock", that requires an understanding of the three dimensional structure of the complex of the catalytic subunit of cAMP-dependent protein kinase, with its very potent specific inhibitor, PKI(5-24).

Disclosed herein is a template gleaned from the crystal structure of the catalytic subunit of cAMP-dependent protein kinase. Just as the chemical information derived from the C-subunit serves as a framework for interpreting the entire kinase family, the structure of cAPK provides information for the creation of a template for viewing the conserved catalytic core of all eukaryotic protein kinases. This invention further provides a model for the identification and design of molecules capable of interacting with the catalytic core of a given enzyme by analyzing the conserved catalytic core of another member of that enzyme class.

X-RAY CRYSTALLOGRAPHY

X-ray crystallography permits three dimensional molecular analysis of a protein at the atomic level. Analysis requires the production of crystals and crystal production requires a pure concentrated product. Further, complexes of a protein of interest together with a second interacting molecule provides information on the conformational changes occurring within a protein in response to that second molecule. X-ray crystallography of a protein with its substrate, an antibody or a drug can provide information for rational drug design.

An X-ray diffraction pattern taken from a crystal looks like an array of spots of varying intensities. Each spot is related to one of the Fourier coefficients of the electron density pattern in the crystal. Thus, the electron density in the crystal can be reconstructed if a sufficient number of diffraction spots can be measured and the relative phase angles of

the Fourier coefficients can be determined. Thus, a crystallized enzyme used in the practice of certain aspects of the present invention should be of sufficient quality to obtain these measurements. For example, the spots of varying intensity in the diffraction pattern decay over time. It is quite difficult to work with diffraction patterns with half lives of less than 10 hours. However, it is possible to work with diffraction patterns having half lives as short as about 15 minutes to 3 hours, depending on the amount of structural data desired to be obtained. Further, it is believed possible to work with crystals of even shorter half lives using equipment and computer programs more advanced than commonly available today. Additionally, not all crystals are of equal quality and poor crystals have large Bragg spacing diffraction limits. Thus, a workable crystal should have a Bragg spacing diffraction limit of less than 4 Å.

Determination of phase angles uses isomorphic replacement to insert atoms into defined positions in the crystal for diffraction data measurement. These angles provide information that permit the production of an electron density map. The map is then used to build an atomic model from which three-dimensional coordinates are measured that define the structure of the crystallized molecule.

MODEL SYSTEM

X-ray crystallography has been employed for the rational design of drugs and other interacting molecules. However, to date, the rational design of affector molecules has been limited to a study of the active site of the protein/affector molecule interaction. Potential affectors designed from this information have not been obtained by looking at interactions beyond the active site. We believe that these interactions assist in binding and thereby contribute to binding specificity. Thus, we have discovered that it is these interactions in concert with information obtained from the active site that make the design of specific affector molecules a possibility. Moreover, this information additionally permits the design of specific affector molecules for related but nonidentical enzymes.

Many enzymes within a cell have evolved from common progenitors. These enzymes share common enzymatic activities and one example is the protein kinase family. Since the functions of the enzymatic families or classes are broadly conserved, at least a portion of the catalytic site is also conserved. Therefore to a large extent rational drug design relies on the identification of the familial similarities and hence drugs are designed to react broadly within a given family or class.

While all members of an enzymatic class may provide a similar activity, such as phosphorylation or dephosphorylation, each member may have only one specific target.

Thus, successful rational drug design based on group similarities would provide molecules that also interact broadly. Where there are many members of an enzymatic class acting specifically within a restricted locale such as a single cell, a broadly acting drug would interact with any number of enzymes from the group. Thus, the interaction would be general and not specific. In contrast, the present invention advantageously is capable of providing affectors with highly specific interactions for a given member of an enzyme class.

Previous methods for rational drug design require the crystallization of the target molecule of interest. However, the production of useful crystals is both difficult and time consuming. It first depends on the ability of the target molecule to be isolated and purified in sufficient quantity for crystallization. A large number of crystallization conditions often need to be tested and once a crystal is made that is of sufficient quality, additional crystals often need to be produced in order to have enough material for analysis. Further, not all molecules are readily purified or readily crystallized. Advantageously, the present invention discloses a method whereby only one enzyme within a family of enzymes need be crystallized.

This invention teaches a method for the identification and design of specific molecules interacting with a specific enzyme wherein the specific enzyme is a member of a broadly acting enzymatic group or class.

The particular enzyme class chosen for this invention is preferably one that has the characteristics generally associated with an enzyme class developed from a divergent evolutionary pathway. That is, an enzyme class in which it is possible to identify similarities within the catalytic core of all members of the class. Enzymes with similar activities that have evolved from convergent evolution will not necessarily share these constant residues and a model or template employing invariant amino acids as anchors would then not be possible. A variety of enzyme families are postulated to arise from divergent evolution, and thus would be expected to serve as a preferred class of enzymes for design of affector molecules within the context of the present invention. Such enzyme families include, but are not limited to, the protein kinases, phosphorylases, and several groups of proteases.

For purposes of illustration only, the present invention is described using the protein kinase family as a model system. As discussed above, these enzymes are essential for many aspects of cell regulation. Over 100 individual protein kinases have been identified. Thus, the successful design of affectors to manipulate the activity of a kinase can provides an invaluable tool for research as well as for the design of a wide variety of therapeutics and diagnostics.

Thus, for example, development of effective specific inhibitors of oncogenic kinases is believed to lead to the development of anti-neoplastic treatments. In addition, specific inhibitors of kinases involved in hormone regulation will be useful in artificially regulating the secretion and regulation of such hormones. Also, since many neuro-transmitters are regulated by kinases, development of new affectors could potentially impact on diseases of the nervous system. Further, platelet aggregation and clot formation might also be regulated through novel affectors of kinases developed through the methods of the present invention. Many other therapeutics are believed possible through the development of novel specific affector molecules.

The model system used in connection with this invention uses cAMP-dependent protein kinase together with a 20 amino acid inhibitor peptide, PKI(5-24), to establish a "lock" for specific affector design. This inhibitor is unique in that it interacts only with the cAMP-dependent protein kinase. Therefore, cocrystallization of this inhibitor with cAMP-dependent protein kinase permits the visualization of the conformation of an enzyme in association with its specific inhibitor.

The general requirements for peptide recognition by the catalytic subunit were characterized originally using synthetic peptides. From those studies evolved a general consensus sequence that includes two basic residues, typically arginine, followed by one intervening small residue preceding the site of phosphotransfer. The phosphate acceptor site, either Ser or Thr, is followed immediately by a large hydrophobic residue. The typical peptide substrate used for this kinase, based on the phosphorylation site in pyruvate kinase, is shown in 1. Replacement of the Ser with an Ala generates an inhibitor peptide with poor affinity. In contrast is the inhibitor peptide, PKI(5-24), derived from the thermostable protein kinase inhibitor (PKI). This peptide, seen in 1, encompasses the consensus sequences described above but also contains additional unique features that convey high affinity binding. The particular features that contribute to high affinity binding were defined using peptide analogues, and the most relevant ones are also indicated in 1. A general structure of the peptide in solution was deduced using circular dichroism (CD) and NMR spectroscopy. The peptide, PKI(5-24), was co-crystallized with the catalytic subunit of cAPK, and the structure of that peptide as well as its interaction with the protein are discussed here.

The folding of the polypeptide chain and the mechanism of catalysis is conserved in all protein kinases. There are 8-9 invariant residues scattered throughout the core for all protein kinases. The crystal structure reveals that most of these invariant residues are

clustered three dimensionally around the site of catalysis providing an interconnected network. The regions involved in peptide recognition extend over a wide area on the surface of the enzyme and until this structure was solved there was no understanding of the details of the peptide recognition sites. The structure of the catalytic subunit thus serves as a framework from which a template for the entire protein kinases family can be produced. This structure provides, for the first time, a true molecular basis for the design of affectors that will selectively target any given protein kinase. Thus, it is an object of this invention to provide a method for the identification and design of molecules interacting with the catalytic core of a protein kinase by preparing a template from the analysis of the catalytic core of the cAMP dependent protein kinase.

The ability to design affector molecules that act on a given enzyme using information obtained by X-ray crystallography is dependent on the formation of crystals of purified enzyme. Methods for crystal production vary greatly and one cannot predict how readily a given molecule or complex will crystalize. However, those skilled in the art will recognize that a variety of methods for crystallizing can be attempted for any given enzyme, and that successful crystallization can be expected of a variety of enzymes. Rational drug design additionally requires information about the interaction of a known affector in order to accurately predict a potential affector's effect on the catalytic core of the enzyme. Thus, crystals of the complex of affector molecule and enzyme together are used to gather information on the conformation of the enzyme in its inhibited conformation. Thus, in addition to information about the catalytic core of an enzyme family and the identification of additional sites adjacent to the core that permit the specific design of inhibitors, the present invention provides an improved method for the crystallization of complexes.

An important feature of certain aspects of this invention is the production of an enzyme/affector template. In order to generate this template, the affector chosen for production of enzyme/affector complex should have a high affinity for a particular enzyme. The initial affector molecule chosen should preferably have a Kd less than 1 μM, and more preferably less than 100 nM, in order to provide a conformation resulting from high affinity interactions. Once the specific interactions are understood it is contemplated that affector molecules having a variety of Kd ranges could be selectively designed for various purposes. Thus, in the model system chosen to illustrate this invention, PKI(5-24) is used as an affector of cAPK, with a Kd of approximately 60 nM. Those of ordinary skill in the art will recognize that other inhibitors with Kd less than 100 nM could also have been chosen to illustrate this aspect of the present invention.

For example, cGMP dependent protein kinase has an inhibitor with a Ki of approximately 6 nM, and an inhibitor for cAPK described by Ricouart et al. is characterized in the 4 nM range (J. Med. Chem., 34: 73-78, 1991). These Ki values are roughly equivalent, however, not identical, to the expected dissociation constants (Kd's).

The PKI(5-24) inhibitor peptide used here is highly specific and is rather large in that it extends beyond the catalytic core. Other known peptides and affector molecules for kinases are not as specific. We have discovered that the interactions beyond the catalytic core provide the high specificity of PKI(5-24) for cAPK.

As stated above, it is the crystallization of the enzyme with its specific inhibitor together with the analysis of the relationship of the inhibitor to both the catalytic core and to areas surrounding the core that provide data for the particular protein kinase "lock". The "lock" comprises the three dimensional structure and ionic, hydrophobic, hydrogen bonding and other interactions of the non-conserved variable residues with the specific affector structure. The lock is defined by the invariant residues of the exemplary structure. When an enzyme of the class is affected by a specific affector, the backbone atoms of these invariant residues must be in substantially the same relative coordinates in all members of the enzyme class. Thus, with knowledge of sequence information of the particular enzyme for which the affector is being designed, knowledge of the lock formed by the invariant residues can be obtained. The coordinates of the invariant residues position the variable residues of the lock in space and thereby permits the design of other specific inhibitors and affector molecules for other protein kinases.

The lock consists of the site of phosphotransfer (P site) with recognition sites for flanking sequences. The flanking sites can be identified by the number of amino acid residues separating that site from the P site. Thus, the first amino acid residue in the direction moving toward the carboxy terminus is designated P+1, and the following residues are designated P+2, P+3, P+4 and so on. Similarly, the residues on the side moving toward the amino terminus are designated P-1, P-2 and so on.

The sites for recognition of the peptide are not identical between members of the protein kinase family, and the chemical content is unique for each given protein kinase. The sequence of the given protein kinase is built into the coordinates of the C-subunit using the invariant residues. The position of these invariant residues can be identified using X-ray crystallographic data, such as the data disclosed herein in Figure 17. This data provides the coordinates for each non-hydrogen atom in cAPK. It is the locations of these invariant residues which serve to define the template common to all protein kinases. This template

can then be used to model the three dimensional coordinates of the variable as a basis to design highly specific affector molecules.

The affector molecules to be designed could be polypeptides, nucleic acids and their analogues, combinations of nucleotides and peptides, organics or any other molecule capable of specific interaction with a given enzyme. The essence of the design of a specific inhibitor for a given protein kinase is based on the three-dimensional fit of the specific inhibitor into the provided "lock", or template, provided by the known structure of cAPK.

The template defined by the invariant or other highly conserved residues can be used to define the region immediately flanking the phosphorylation site and, in addition, can incorporate more distant parts of the molecule to enhance specificity and affinity. The peptide recognition site serves in the same manner as the antigen recognition site of an antibody. This site extends over a large surface of the enzyme and provides a unique lock for the design of a wide variety of affector molecules, including both peptide and non-peptide affectors. Each particular protein kinase has a different and unique chemical content at each individual site. Thus, the "lock", is unique for each protein kinase.

The "lock" of any particular enzyme represents a topological map with defined sites, positions of which vary between members of the enzyme class. As an analogy, each kinase can be thought of as functioning in a manner similar to a specific antibody in that it recognizes only a very specific set of proteins to phosphorylate. However, each of the kinases has a conserved template, the positions of which will not substantially vary between kinases in an inhibited conformation. Thus, using computer modelling together with known sequence information regarding a particular kinase, the invariant residues of the kinase can be placed in the template conformation, and the approximate positions of the variable residues can be predicted.

The lock provides the information from which other specific affector molecules can be designed. It provides information on topology, charge interactions and the points of contact both within the catalytic core and around the core that suggest the design features important for the production or identification of novel affector molecules. Thus, the goal is to design an affector having homologous topography and charge fields that complement the catalytic core of the lock of the enzyme. Computer modelling can be used with these factors to design an affector capable of inducing a conformation where the conserved amino acid residues of the enzyme are in homologous locations to the template.

BRIEF DESCRIPTION OF AFFECTOR DESIGN

The basic steps toward achieving this invention are provided briefly here and in detail below. A class of enzymes is first identified wherein at least one enzyme of the class has a highly specific affector molecule. Then the inhibitor is tested for specificity and, preferably, the inhibitor sequence is reduced in size until a minimum sequence having the desired specificity is obtained. Sequence data from related enzymes is analyzed so that a consensus region that forms the catalytic core can be identified. Crystals of affector molecule together with the model enzyme are subjected to multiple isomorphous replacement techniques to prepare heavy atom derivatives. This permits the location of heavy atoms within the structure to be identified and additionally permits multiple diffraction patterns to be combined to deduce phase angles for calculation of the electron density of the structure. Those of ordinary skill in the art will recognize that other techniques can be used to deduce phase angles and to improve the accuracy of previously deduced phase angles.

A three-dimensional structure can be obtained from the electron density data using a computer program such as TOM/FRODO. Further, a computer program, such as X-PLOR, can be used to improve the accuracy of the initial three-dimensional structure. There are a variety of computer programs available for analyzing X-ray crystallographic data. Those used in the development of the model system for this invention are cited herein. Those of ordinary skill in the art will recognize that many other such computer programs providing similar functions could also have been used. From this data, the points of contact are identified both within the catalytic core and the surrounding region. Invariant amino acids and consensus recognition sequences are identified. The data is further analyzed against available chemical data such as NMR, CD, SANS data and other data resulting from chemical procedures. This chemical data can provide additional information for the structural model.

The coordinates of the invariant amino acids residing in the conserved catalytic core and the surrounding invariant residues in the enzyme/affector complex provide the template to be duplicated in other members of the enzyme class. The lock of the enzyme for which the affector is to be designed is then built by replacing the variable amino acids of the catalytic subunit of the template enzyme with the amino acids of the new enzyme. Any gaps in the sequence alignment between the enzyme used to generate the template and the enzyme for which the lock is being modelled generally occur within loops. These loop regions can be modelled separately using the structural data accumulated in a data bank, such as the Brookhaven data bank. The model of protein kinase can then be corrected and

refined using an energy minimization procedure and using molecular dynamics to eliminate stearic and electrostatic clashes. The resulting model of the catalytic core of the protein kinase under investigation is then inspected for amino acid content of the enzyme's surface which interacts with the proposed inhibitor.

In accordance with one aspect of the present invention, another member of this enzymatic class can then be analyzed in the context of this template. If the new enzyme can be crystallized, then the information obtained from the crystallization is merged with the "lock" structure. However if the new enzyme is not accessible or is not crystallizable, the enzyme can still be incorporated into the three-dimensional lock. The ability to incorporate the new enzyme into the template is dependent on the identification of conserved residues within the catalytic core of the new enzyme that are complementary to the conserved residues in the model enzyme. The template establishes the coordinates for these residues in three-dimensional space as well as providing coordinates for the three-dimensional surface of the catalytic core and adjacent regions.

For cAPK and the protein kinase family, the invariant residues are identified and summarized in the review by Hanks et al., supra. The template permits a comparison of the new enzyme catalytic core surface with cAPK. Residues within the catalytic core that are different from those of cAPK are studied to determine how those differences in the new enzyme might alter the surface of the core or change the structure of a new affector molecule. Recombinant cAPK can then be subjected to site-directed mutagenesis to change residues specific to cAPK into residues found in the new enzyme. This recombinant protein can be crystallized.

A novel affector molecule can then be synthesized that complements the electrostatic charges and topography of both the catalytic core and identified surrounding regions of interest for the new enzyme. The points of contact, hydrophobic pockets, site of phosphotransfer, topography and stearic interactions are assessed and the affector molecule can then, if necessary, be subjected to random mutagenesis or site-directed mutagenesis to improve the affector/enzyme interaction. This model affector molecule together with recombinant mutated cAPK, are tested with the target enzyme for affector activity. The affector molecule is finally tested with the native new enzyme. Fluorescent tags bound to the affector can be used to assess binding to the new enzyme in the cell. Alterations in enzyme function can be detected by gel electrophoresis and complexes of enzyme and affector can be isolated and purified for further analysis. Thus, new enzyme purification and crystallization is not required for affector design.

As discussed above, generation of new affectors is not limited to peptides. A variety of chemically synthesizable compounds can be used.

The model can be tested by a variety of methods. For example, kinetic determination of inhibition constants of novel inhibitors can be measured. Also, CD, SANS and other chemical procedures can be used to assess the extent of the conformation changes due to binding of the affector. If a mutated form of the enzyme has been prepared, cocrystallization of the affector with this mutated form can be performed and the points of contact can be determined and compared with the modelled points of contact.

ENZYME FAMILY CHOICE AND IDENTIFICATION OF CATALYTIC CORE

This invention relates particularly to enzyme families formed by divergent evolution. Once an enzyme family of interest is identified, an individual enzyme is chosen from a group of enzymes that share invariant residues within their postulated active sites.

The enzymatic or active site within a given protein kinase can be broadly identified through biochemical means. When the enzyme exists as a group of subunits, enzymatic activity is often restricted to one of those subunits. Thus, prior to performing these biochemical means, the enzymatic subunit can be purified from the holoenzyme. The active site can be further localized by systematically reducing the subunit size and assessing enzyme activity with each reduction. In one method, the various mRNA sequences encoding the related enzymes are reversely transcribed and cloned. Sequence information can then be obtained from the catalytic region for a number of enzymes of the same class. Similar amino acid residues within the catalytic subunit are aligned in order to visualize homologous regions. Invariant amino residues can be identified among the class which are either present in all known members of the class or substantially all members of the class. At least a plurality of these invariant residues are believed necessary for enzyme activity within the catalytic subunit. Thus, the invariant residues can further define the catalytic core.

For the protein kinase family, invariant amino acid residues are located within the catalytic core and are boxed in by a solid line in Figure 1. Figure 1 illustrates the general topological arrangement of the catalytic subunits from a number of protein kinases.

Figure 2 illustrates that while the catalytic regions from members of the protein kinase family share some striking similarities, the placement of this active region within the enzyme, the size of the enzyme and the regulatory regions of the enzyme vary considerably. The conserved catalytic core is denoted in Figure 2 as solid black areas and regulatory regions are cross-hatched. Additional information regarding the use of cAMP-dependent

Protein Kinase as a model for the protein kinase family can be found in a review by S. Taylor (J. Biol. Chem. 264:8443-8446, 1989.).

It is known from an analysis of the catalytic core of the protein kinase family that the core is included in a conserved 300-residue segment. Site-directed mutagenesis of recombinant enzyme sequences has been used to identify particular residues critical to enzymatic function. In the cAMP-dependent kinase an invariant lysine residue at position 72 has been shown to be important by site-directed mutagenesis and a triad of glycines is thought to be associated with ATP-binding.

The enzyme exists as a tetrameric holoenzyme composed of a dimer of regulatory subunits and two catalytic subunits. cAMP binds to the regulatory dimer yielding dissociation of the enzyme into an $R_2(cAMP)_4$ complex and two active catalytic (C) subunits. It is the active C-subunit that phosphorylates serine or threonine residues on substrates having the consensus sequence Arg-Arg-X-Ser/Thr-Leu.

AFFECTOR MOLECULE FOR TEMPLATE DEVELOPMENT

In a preferred form of the present invention, the enzyme used to establish the template or lock is, advantageously, a molecule that binds with high affinity to its affector, preferably with a dissociation constant less than 1 μM. For example, there are many such known affectors, such as inhibitors and activators, of various protein kinases. Kinases with a regulatory subunit are known that are inhibited by a peptide encoding the regulatory subunit binding site. Similarly, kinases that possess an autoinhibitory portion are also known. Thus, for such a kinase, this autoinhibitory region could be cleaved away from the core enzyme, purified and analyzed to provide a minimal high-affinity inhibitory sequence.

There are several inhibitors of cAMP-dependent kinase. The regulatory subunits can function as physiologic inhibitors as can the heat stable inhibitor protein (PKI). These inhibitors share a substrate-like sequence based on the arginine doublet, N-terminal to the position of the phosphorylation site in a normal substrate. Peptide fragments containing the consensus sequence bind the C-subunit in a manner analogous to a real substrate. PKI has an alanine in place of the phosphorylatable residue. While the PKI sequence is clearly inhibitory, the addition of a 15 residue stretch N-terminal to PKI increases inhibitory activity. Thus, residues external to the catalytic site are believed to be relevant in providing potent, high-affinity, inhibition and for improving the specificity of an inhibitor.

A protein that is a high-affinity inhibitor of an enzyme can be dissected to find a smaller fragment, if it exists, that still contains high-affinity inhibitory activity. At least three factors are useful in this dissection: 1) an ability to produce chemically defined fragments

of the larger inhibitor, either by synthesizing peptides or by cleaving the inhibitor with reagents such as cyanogen bromide or proteases, that cut at short amino acid sequences of a specific type for each reagent, 2) an ability to isolate specific fragments of the larger inhibitor from the mixture of fragments resulting from cleavage of the larger inhibitor, and 3) an ability to assay chemical species for inhibition of the enzyme of interest.

To carry out the isolation of a potential smaller inhibitory region of a larger inhibitor, one can cleave the inhibitor into fragments using a protease. Then one can separate the resulting fragments using HPLC and assay the fractions for high-affinity inhibition of the target enzyme. If no fraction is found that exhibits the desired inhibition, the cleaving reagent may have cleaved at a location that splits the inhibitory portion of the protein, destroying its ability to inhibit. In this case, it would be desirable to obtain other cleavage patterns until an inhibitory fragment is found. After obtaining the smallest possible inhibitory fragment using proteolytic cleavage of the intact inhibitor, one can chemically sequence the fragment as a step toward further defining the smallest fragment still having high-affinity inhibitory activity. With knowledge of the amino acid sequence, one can then use peptide synthesis to construct progressively shorter subsets of this fragment. These shorter subsets can then be assayed for inhibitory activity. Proceeding in this manner will thus allow definition of the smallest sequence, present in the larger inhibitor that still possesses high-affinity inhibitory activity toward the target enzyme. Methods for determining inhibition constants for tight-binding inhibitors are found in Biochem. J. 127: 321-333, 1972 by P. Henderson. Methods for determining the inhibitory region PKI(5-24), are provided by Scott et al. in Proc. Natl Acad. Sci. USA 82:4379-4383, 1985.

OBTAINING THREE DIMENSIONAL STRUCTURE DATA

In order to obtain data on the conformation of the template of the enzyme formed by binding of the affector thereto, a variety of techniques can be used. These techniques include, circular dichroism, small angle neutron scattering, diffraction methods, including any combination of multiple and single isomorphous replacement, single or multiwavelength anomalous scattering methods, molecular replacement methods maximum entropy phasing, solvent-flattening methods and so-called "direct" methods used primarily to solve small-molecule structures. However, in the preferred embodiment, X-ray crystallography is used in order to generate specific coordinates for each of the non-hydrogen atoms in the complex. Coordinates for the hydrogen atoms could additionally be obtained using neutrons. Thus, following the isolation of an exemplary protein and affector and following or during the sequence analysis of related enzymes, crystals of enzyme and affector protein are generated.

The crystals can be generated from enzyme purified from natural tissue or from enzyme generated by recombinant means. Provided below are examples pertaining to the production of crystals using the recombinant mouse C_α-subunit of cAMP dependent protein kinase and purified cAMP-dependent protein kinase from porcine heart. Nelson et al. describe the purification schemes for porcine heart cAMP dependent kinase (J. Biol. Chem. 256:3743, 1981.) and Slice et al. disclose the methods for the generation of recombinant mouse C_α-subunit in E. coli (J. Biol. Chem. 264:20940, 1989). The sequence data for cAPK was published by Uhler et al. (J. Biol. Chem. 261:15360-15363, 1986).

The steady state kinetics of the C-subunit, purified from E. coli are identical to the mammalian C-subunit, although the E. coli protein is more labile to heat denaturation. Unlike the mammalian enzyme, the recombinant C-subunit lacks a myristoyl group at its amino terminus. For a review of protein crystallography see Protein Crystallography, 1976, T. Blundell and L.N. Johnson, Academic Press, New York. Information on circular dichroism and neutron scattering is found in Biophysical Chemistry. Part II: Techniques for the Study of Biological Structure and Function, C.R. Cantor et al. (W.H. Freeman and Co., San Francisco, 1980).

Example 1

Porcine Heart C-subunit Crystal Forms

Reagents were obtained from the following sources: threo-1, 4-dimercapto-2,3-butanediol (DTT, dithiothreitol; Aldrich, Milwaukee, WI); N,N-bis(2-hydroxyethyl)glycine (Bicine; Aldrich); methanol (Fisher Scientific); ammonium acetate (Aldrich); polyethylene glycol (Dow, Midland, MI).

The peptide inhibitor PKI(5-24) was synthesized at the La Jolla Cancer Research Foundation (La Jolla, CA) and modified in our laboratory These modifications are described in detail below. The sequences of the peptide inhibitors are: (1)PKI(5-24); TTYADFIASGRTGRRNAIHD, (2)PKI(5-24), tyrosine iodinated: TTY*ADFIASGRTGRRNAIHD. The peptide sequence abbreviations follow either of the two standard abbreviation schemes for amino acids; the three letter code or the single capital letter designation. Both are standard abbreviations and are well understood by those of skill in the art.

The porcine C-subunit was purified to a single band on SDS-polyacrylamide gels and used for crystallization. Two crystal forms were prepared. Photographs of the porcine heart apoenzyme (cubic); and the porcine heart C:MgATP:PKI(5-24) ternary complex (hexagonal) are provided as Figures 18A and 18B.

The first crystal form used the hanging-drop vapor diffusion method. A drop of protein mixed with precipitating agents is suspended from a microscope cover slip and allowed to equilibrate through the gas phase against a larger reservoir.

Specifically, 30-μL drops of 3-4 mg/mL protein solution were suspended and allowed to equilibrate against approximately 1mL of reservoir solution in wells of plastic Linbro tissue culture trays over a time of several days to weeks. Both new forms, as well as the earlier $P2_1$ form, were grown at 4°C. The porcine heart C-subunit was concentrated to 8-12 mg/mL and subjected to a final dialysis before attempting crystallization. The specific recipe for obtaining the first new form was the following: drop- 1/3 protein in 50 mM $(NH_4)_2HPO_4$ and 5 mM 2-mercaptoethanol (pH 8.0-8.2); 1/3 150 mM NH_4CH_3COO, 50 mM $(NH_4)_2HPO_4$, and 10 mM dithiothreitol (DTT) (pH 8.1-8.2); and 1/3 reservoir composed of 8-9% PEG-400, 17-20% MeOH, and 10 mM DTT. Crystals of the second form were obtained from the same conditions as the first new form when the drop contained, in addition to the protein, MgATP and a 20-residue peptide inhibitor [PKI(5-24)] in the molar ratio 20:5:1:1 ATP:Mg^{2+}:PKI(5-24):C-subunit. The same crystal form was subsequently grown from a drop containing 1/3 protein in 50 mM bicine, 100 mM NH_4CH_3COO, and 5 mM 2-mercaptoethanol (pH 8.3); 1/3 MgATP and PKI(5-24) in 10 mM DTT in the same ratio to protein as before; and 1/3 8 mM DTT and 8% PEG-400. The reservoir contained 8% PEG-400, 15-20% MeOH and 7mM DTT. The first new crystal form could also be grown in the presence of the Mg^{2+} and the non-hydrolyzable ATP analogue adenosine 5'β, γ-methylenetriphosphate (AMP-PCP). The second new crystal form, representing the ternary complex, could be grown with $CoCl_2$ or $CdCl_2$ substituted for $MgCl_2$ in the crystallization. The transition from one crystal form to another caused only by addition of MgATP and the peptide inhibitor PKI(5-24) suggests that a significant conformation change may occur upon their binding.

The space groups of the new crystal forms were determined to be $P4_132$ (cubic) (Figure 18A), and $P6_122$ (hexagonal) (Figure 18B), respectively. Space groups were determined and all diffraction data were measured at the University of California, San Diego Research Resource Laboratory at 4°C using graphite-monochromated CuK_α X-rays from either the Mark II Elliot GX-6 rotating anode diffractometer operating at 2 kilowatts or the Mark III Rigaku RU-200 rotating anode diffractometer (available from Rigaku USA, Danvers, MA) operating at 5 kilowatts, each equipped with two Xuong-Hamlin multiwire area detectors (available from San Diego Multiwire Systems, San Diego, CA).

Preferably, area detector data collection is used. One facility offering equipment to support this data collection technique is The Resource Research Laboratory. This facility is a geographically designated, NIH supported facility to promote the use of X-ray crystallographic techniques. In speed, signal-to-noise ratio, and data precision, area detector data collection far surpasses standard diffractometer or film data collection. On the average, data collection is 50 times faster; consequently complete high resolution data sets can frequently be collected from a single crystal in one or two days. The space groups and lattice constraints of the crystal forms were determined to be the following: $P4_132$, a=b=c= 169.24 Å; and $P6_122$, a=b=80.3 Å, c=293.0 Å. Calculations using an average reciprocal density of 2.7 $Å^3$/D yield to the nearest unit 2 and 1 C-subunit monomers/asymmetric unit. The $P4_132$ form diffracts typically to 3.2 Å. Pictures of the cubic and hexagonal crystal forms can be seen in Figure 18

Because the $P6_122$ crystal form had diffraction better in extent and decay characteristics than the $P4_132$ form and because of the greater biochemical interest of a ternary complex, work concentrated on solving the hexagonal ternary complex crystal form. The lack of phase angles for a similar protein structure prohibited an initial structure solution for the C-subunit in the $P6_122$ form using molecular replacement techniques, so a structure solution using standard multiple isomorphous replacement (MIR) techniques was attempted. Both of these are techniques known to those of ordinary skill in this art. Briefly MIR involves introduction into the space group asymmetric unit of a relatively heavy reference atom that, after being located through difference Patterson analysis, enables the needed phase angles to be determined. The reference atom can be found with 6-Å data, and with its location and generation of phase angles the fundamental crystallographic problem of a protein structure solution is solved and an electron density map can be calculated. Subsequent work on a protein structure focuses on incrementally improving the degree of detail visible in the electron density map through acquisition of higher resolution data and accompanying phase angles.

The procedure used to search for heavy-atom derivatives was to soak or co-crystallize C-subunit with heavy atoms based on the empirical success record or various heavy atom reagents and on known C-subunit chemical information, such as the availability of two free thiol groups and the obligatory use of a divalent cation in catalysis. Soaks in Au, Hg, and Pt compounds yielded precession picture diffraction changes but uninterpretable 6A difference Patterson maps. A 4.8-Å data set from a $Na_2U_2O_7$ soak yielded an apparent Patterson solution through examination of isomorphous difference and (1/variance)-

weighted anomalous difference Patterson maps, but the site quality was not high and attempts to reproduce or improve the soak failed. Isomorphous crystals grown with Co^{2+} or Cd^{2+} substituted for Mg^{2+} proved useless since neither metal could be located (location of Co^{2+} through Patterson analysis was improbable anyway due to its lightness), although with phases their positions could reveal metal site number and location. Co^{2+} and Cd^{2+} were chosen for co-crystallization based on their reported ability to support nucleotide binding to the C-subunit and support catalysis, although at a reduced rate.

The single most important modification in the crystallization protocol that led to the formation of crystals in a different space group was the careful selection of polyethylene glycol in combination with various low molecular-weight alcohols. Commercially available polyethylene glycol contains various contaminants that may cause problems in the achievement of stable and reproducible crystallization conditions. All commercially available polyethylene glycols (PEG) were examined with the aim of detecting the presence of ionic species.

The lowest level of ionic contaminants was detected in PEG manufactured by Dow Chemical. It is this PEG that was selected for further crystallization experiments. PEG from other sources appeared to be generally more contaminated and also exhibited large differences in contamination between batches. In our experiments, several molecular weights of PEG were used along with several low-molecular-weight alcohols.

The catalytic subunit crystallized in the hexagonal space group with the introduction of PKI(5-24) and MgATP, whereas in its apo form it crystallized in the cubic space group using otherwise identical crystallization conditions, indicates that the hexagonal crystal may arise as a result of a different conformational state of the enzyme.

Example 2

Mouse recombinant C-subunit Crystal Forms

One of the most promising directions for combining crystallographic methods with those of molecular biology is the development of highly effective vectors for expressing large amounts of protein for crystallization. Expression of protein in E. coli also provides a mechanism for eliminating posttranslational modifications which may hinder crystallization and in addition permits structure-function studies on mutant forms of the protein following the generation of mutant containing crystals.

The recombinant murine catalytic subunit, whose expression and purification was described by Slice et al., is devoid of myristic acid at the N terminus and differs by nine amino acids from the porcine heart catalytic subunit used in the earlier crystallizations. It

has been shown, however, that N-terminal myristoylation is not necessary for C-subunit function. Additional differences between the porcine heart and recombinant mouse C_α proteins include the presence of additional phosphorylation sites (Ser 10 and Ser 139) on the recombinant protein.

Crystals were prepared from a binary complex of the recombinant mouse C_α-subunit with a bound, high-affinity (K_i = 3 nM) inhibitor peptide. The peptide (PKI95-24) derived from the N-terminal region of the naturally occurring thermostable protein kinase inhibitor protein (PKI), is the same peptide inhibitor used for the porcine heart ternary complex crystal. The steady state kinetics of the C-subunit purified from E.coli, are indistinguishable from those of the mammalian C-subunit, although the E. coli protein is more labile to heat denaturation.

The recombinant protein was crystallized using a small variation of the porcine heart ternary complex (hexagonal) conditions. A photograph of an exemplary crystal is provided in Figure 18C. First a ternary complex was prepared with MgATP and PKI(5-24). A C:PKI(5-24) binary complex was obtained after small-angle neutron scattering experiments showed that for the recombinant mouse C-subunit, the PKI(5-24) peptide alone, without MgATP, was able to cause a significant decrease in the radius of gyration. The ternary complex crystal form diffracted to at least 2.7 Å on the Mark III and was of orthorhombic space $P2_12_12_1$. A data collection strategy following the procedure of Xuong, et al., (Acta Cryst. B41: 267, 1985 was developed. Equipment for use with this procedure is available from San Diego Multiwire Systems of San Diego, California. The procedure allowed an asymmetric unit of data to be collected in 3 ω-sweeps totaling about 140° (with appropriate choice of ϕ and χsettings and a crystal mounted with one of the axes parallel to the capillary axis). Data collection took about 16 h for a >90% complete 2.7-Å data set from one crystal with R_{sym} on the intensity of 4-6%; in the same period the average reflection intensity decayed approximately 15%.

Crystals were generally soaked or mounted in a stabilizing solution prepared as the crystallization drop, but with the addition of the initial reservoir MeOH percentage and the omission of C-subunit and PKI(5-24). It was discovered that Cd^{2+} could be substituted for Mg^{+2} in crystal growth, as with the porcine heart ternary complex crystal. It was also discovered that elevating the $MgCl_2$ to ten times the starting mother liquor concentration, after crystal growth had stopped, altered the cell dimensions slightly (<1%) and resulted in a different pattern of heavy-atom binding.

Example 3

Recombinant Binary-Complex Structure Solution

The binary complex crystal was nearly isomorphous with the ternary complex crystal, differing by less than 1% along any axis and had the same space group with a=73.62 Å, b=76.53 Å, c=80.14 Å. The asymmetric unit contains one C:PKI(5-24) complex and has a calculated solvent content of 0.53. Mercury reagents were co-crystallized with the C:PKI(5-24) complex by exposing it to 1-mM reagent for six hours, followed by dialysis to remove excess Hg reagent. Native and co-crystallized 4-(hydroxymercuri)benzoic acid (PHMB) derivative diffraction data were measured on the Mark III diffractometer. Data from two native crystals were merged to provide a more complete data set for the initial phase computation, phase extension work, and initial refinement cycles, but later refinement used data from only a single crystal that yielded better quality data. Data from two PHMB co-crystals, one with measured Bijvoet mates, were kept separate and used to compute initial phases, which were improved at constant 3.5-Å resolution using the solvent flattening approach of Wang (Methods Enzymol. 115:90, 1985), with a slightly conservative solvent content of 0.50. Additional phases from inversion of the solvent-flattened map were added incrementally using 6 additional envelopes to a final resolution of 2.7 Å. Starting with minimap α-carbon coordinates, the program TOM/FRODO (available from Christian Cambillau, University of Marseille, Marseilles, France) was used with the resulting map to model in the sequence of PKI(5-24) and 257 of the 350 residues in the C-subunit. This partial model was refined using X-PLOR (available from Axel T. Brunger, Yale University, New Haven CT), and calculated structure factors were combined with Wang structure factors in a resolution-dependent manner using equally weighted ABCD coefficients to yield improved maps. ABCD coefficients are described by Hendrickson et al. (Acta Cryst. B26: 136, 1970). Structure solution statistics are summarized in 2, and a sample of electron density of the structure determination is shown in Figure 3, described in detail below.

A number of crystal forms of the catalytic subunit of cAPK have been obtained thus far. All of the crystal forms of the different complexes of the catalytic subunit, with the exception of the monoclinic crystal of the apoenzyme, were obtained under identical crystallization conditions and these are described above. The crystals in different space groups therefore very likely result from conformational states of the enzyme. Crystals of both the binary and ternary complexes with PKI(5-24) exhibited better diffraction characteristics than crystals of the apoenzyme.

Our results also indicate that the ternary complex of the murine catalytic subunit expressed in E. coli produced a crystal of better quality than did the ternary complex of the

catalytic subunit purified from porcine heart. It is difficult to conclude whether this was due to the absence of myristic acid, the amino acid differences between the two forms, microheterogeneity in the mammalian enzyme, or a combination of these factors. It may suggest, however, that another way to improve the quality of crystals is to mutate the protein and to cocrystallize mutants if crystallization of the wild type fails.

Three factors are important for reproducible crystallization. First, the salt of the eluting buffer of the last column must be chosen carefully. Second, the purity of the protein must be verified with isoelectric focusing gels. The protein must not contain typical additives, such as glycerol and should not be frozen prior to crystallization. Third, all reagents used for crystallization must be of the highest degree of purity. If all of these conditions are met, it is possible to obtain, in identical crystallizations, three different crystal forms representing two different conformational states of the enzyme. Some of those crystals, such as those of the ternary complex with PKI(5-24), are of much better quality than the other crystals.

The current model consists of C-subunit residues 15-350 and 1-20 of PKI(5-24) and has been partially refined using X-PLOR to an R-factor of 0.195 with r.m.s.(root mean square) bond length deviation from ideality of 0.024 Å. The location of the MgATP-binding site was determined by difference Fourier synthesis with the nearly isomorphous ternary complex crystal, which showed clear density for the adenine, ribose, and α-PO_4 for the low-[Mg^{2+}] ternary complex crystal. The high-[Mg^{2+}] difference density showed additional features that could contain the β- and γ-PO_4 as well as metal ion(s), but an unambiguous assignment of atoms to this density could not be made.

Diffraction data is summarized in Table 1. Definitions for Table 1 are as follows:f_h, calculated heavy-atom structure factor amplitude; F_p, measured native structure factor amplitude; F_{ph}, measured derivative structure factor amplitude; ΔF_{anom}, calculated Bijvoet difference; E_{iso}, r.m.s. isomorphous lack-of-closure, E_{anom}, r.m.s. anomalous lack-of-closure; $R_c = \Sigma||F_{ph} \pm F_p| - f_h|/\Sigma|F_{ph} - F_p|$.

All diffraction data were measured at 4°C using graphite-monochromated CuK_a X-rays from the Mark III Rigaku RU-200 rotating anode diffractometer equipped with two Xuong-Hamlin multiwire area detectors. Paired runs starting from settings (ω,ϕ,χ) and (ω,ϕ+180,-χ) were used to collect Bijvoet mates (inverse beam method). Data reduction and derivative-to-native scaling were done using the UCSD area detector data processing programs (available from San Diego Multiwire Systems). $R_{sym} = \Sigma|I_{obs} - I_{avg}|/\Sigma I_{avg}$ and is shown for merged Friedel pairs.

Native-1 was used for native. Hg positions of the PHMB (4-(hydroxymercuri)benzoic acid) co-crystal derivative were found from a difference Patterson synthesis. The heavy-atom sites in relation to the model suggest heavy-atom binding at Cys 343 (major site) and Met 58 (minor site). Positional and relative occupancy refinement of two common sites (relative occupancies 2.66, 1.87 for PHMB-1), and calculation of native phases and corresponding ABCD coefficients, were done using the program HEAVY (available from the Protein Data Bank, Brookhaven National Laboratory, Upton, NY). Solvent flattening used the Wang program package (Bi-Cheng Wang, University of Pittsburgh, Pittsburgh, PA) on imported initial ABCD coefficients and phases to 3.5 Å. Molecular envelopes were calculated with solvent content 0.50 rather than 0.53 calculated for the cell. After 3 envelopes at 3.5 Å, the resolution was extended incrementally in 6 shells to a final resolution of 2.7 Å. After convergence at 3.5 Å, the mean phase change/reflection was 36.6° and the mean figure of merit was 0.84; the map inversion R-factor was 0.181. Phase extension added 6786 phases from 5914 in the 3.5-Å starting set; 261 unobserved reflections were estimated by map inversion in the 2.7-Å set.

X-PLOR Version 2.1 was used exclusively following recommended protocols provided in the accompanying manual. Simulated annealing was performed according to a slow-cooling protocol (Brunger et al. Science 235:458-460, 1987) between either 3000K or 4000K and 300K, followed by 120 cycles of conjugate-gradient minimization. Refinement began with the partial model of Stage A to improve the coordinates for phase combination. Combined maps were calculated using the Hendrickson-Lattman scheme. Wang phases were used to 6 Å combined ones between 6 Å and 3.5 Å or 3.0 Å, and calculated phases between 3.5 or 3.0 Å and 2.7 Å. The corresponding weighted amplitudes were $m_{Wang}Fo$, $m_{comb}(2Fo\text{-}Fc)$, and $m_{sim}(2Fo\text{-}Fc)$. The model was completed by iterative refinement and building in areas not included in refinement of partial model. Refinement and R-factor ($= \Sigma|F_o\text{-}F_c|/\Sigma F_o$) calculations used $F/\sigma > 2$ reflections (12024 Native-1 reflections; 10194 Native-2 reflections beginning with Stage B). The current R-factor of 0.195 is for 2939 atoms (no solvent atoms) with individual B-factors (r.m.s. B = 17.6 $Å^2$). R.M.S. bond length and angle deviation from ideality are 0.024 Å and 4.3°.

In summary, the crystals were grown as described above using a 5-10% molar excess of PKI(5-24) and were determined to be of space group $P2_12_12_1$ with a = 73.62 Å, b = 76.52 Å, c = 80.14 Å. The asymmetric unit contained one C:PKI(5-24) complex and had a calculated solvent content of 0.53. Native and co-crystallized 4-hydroxymercuri)benzoic acid (PHMB) derivative diffraction data were measured using Xuong-Hamlin area detectors.

Data from two native crystals were merged to provide a more complete data set for the initial phase computation, phase extension work, and initial refinement cycles, but later refinement used data from only a single crystal of better quality. Data from two PHMB co-crystals, one with measured Bijvoet mates, were kept separate and used to computer initial phases, which were improved at constant 3.5-Å resolution using the solvent flattening approach of Wang with a slightly conservative solvent content of 0.50. Additional phases from inversion of the solvent-flattened map were added incrementally using 6 additional envelopes to a final resolution of 2.7 Å. Starting with a minima alpha-carbon coordinates, the program TOM/FRODO was used with the resulting map to model in the sequence of PKI(5-24) and 257 of the 350 residues in the C-subunit. This partial model was refined using X-PLOR, and calculated structure factors were combined with Wang structure factors in a resolution-dependent manner, using equally weighted ABCD coefficients to yield improved maps. Details on the combination can be found in Allured et al. Proc. Natl. Acad. Sci. USA 83:1320, 1986 and Remington et al. J. Mol. Biol. 158:111, 1982. An example of the electron density of the structure determination is shown in Figure 3.

Figure 3 is a stereo view of the electron density for the structure determination. Portions of the latest refined model of 3 β-strands are shown (top to bottom from left): 112-106, 114-121, 75-69. Figure 3A provides the 1.5-σ experimental density calculated to 2.7Å using phases after Wang improvement and extensions. Figure 3B provides the 1.5-σ($2F_o$-F_c) density calculated with 10 to 2.7-Å refined model phases. The current model consists of C-subunit residues 15-350 and 1-20 of PKI(5-24) and has been partially refined using X-PLOR to an R-factor of 0.-195 with r.m.s. bond length deviation from ideality of 0.024Å. The structure of the catalytic subunit and affector molecule are described below.

Example 4

Structural Analysis of the Catalytic Subunit

A stereo view of the backbone structure of the C-subunit with the bound peptide is shown in Figure 4. Residues 15-350 of the C-subunit and the twenty residues of PKI(5-24), in bold print, of the partially refined model are shown. The overall dimensions of the monomer (65Å x 45Å x 45Å) indicate a slightly elongated molecule. Earlier hydrodynamic measurements showing a Stokes radius of 26.1Å, a frictional coefficient ration (f/f_o) of 1.19, and a radius of gyration of 20Å are consistent with this structure. The most striking feature of the overall molecular architecture is its bilobal shape with a deep cleft between the two lobes. The core of the small lobe is associated primarily with the amino-terminus, while the core of the large lobe corresponds to the C-terminal region of the protein. The cleft

between the lobes is filled by a portion of the bound inhibitor peptide in the binary complex. A difference Fourier map of the ternary complex containing both peptide and MgATP places MgATP at the base of that cleft (Figure 5). The 3.5-σ positive density contours for the ($F_{ternary}$-F_{binary}) difference Fourier were calculated using refined model phases in 10 to 2.7-Å range and are shown superimposed on the partially refined backbone model. Figure 5A illustrates the general localization of MgATP while Figure 5B is a close-up of difference density enclosing an oriented model of AMP.

The cleft is clearly the site of catalysis, and the peptide-induced conformational changes, observed by both SANS and circular dichroism, may be associated with a closing of this cleft. SANS established that in the absence of inhibitor and MgATP the enzyme adopted a more expanded conformation than that adopted by the enzyme in the binary complex of the enzyme and the peptide inhibitor, or the ternary complex of the enzyme, inhibitor and MgATP. This technique was also used to show that binding of the inhibitor to the enzyme did not require MgATP. Neutron scattering, in particular, established that the apo form of the enzyme adopts a more expanded conformation than the ternary complex containing MgATP and PKI(5-24). Furthermore, PKI(5-24) alone, but not MgATP, was sufficient to induce this conformational change. SANS and CD are techniques known to those of ordinary skill in this art. Accordingly, no further descriptions of these techniques are necessary.

Most of the predictions of secondary structure made prior to this crystallographic study of the C-subunit are quite inaccurate and do not correlate well with the actual structure that is provided herein. The prediction of the secondary structure by Benner et al., Adv. Enzyme Regulat. 31:121, 1991, is somewhat more accurate. It is based on chemical information and homologies within the protein kinase family and is accurate within the small lobe. However, detailed and accurate information on the structures of the protein kinase family has not been available until the discoveries presented herein.

The amino-terminus of the C-subunit begins with an amphipathic α-helix that lies primarily along the surface of the larger lobe. This N-terminal region differs in the recombinant and mammalian enzymes, since the recombinant protein lacks a myristoyl group at the N-terminal glycine. In the crystal structure, the first 14 amino acids are not visible. However, the surface of the enzyme in this N-terminal region is hydrophobic, suggesting a possible site for the N-terminal myristoyl moiety of the mammalian enzyme. The myristoyl group stabilizes the C-subunit but does not promote association with membranes.

The smaller lobe, consisting of residues 40 through 125, is associated primarily with the binding of the nucleotide and is characterized by a dominance of β structure. Five antiparallel β-strands comprise the core of this domain. The only helical element in the small lobe is inserted between β-strands 3 and 4 and lies on one side of the plane of the β-sheet. It consists of two parts: a two turn helix B, followed by a sharp break and a five turn helix, helix C. Based on a difference Fourier map (Fig. 5) with a ternary complex of the recombinant C-subunit containing MgATP and PKI(5-24), and supported by chemical evidence discussed below, it is clear that this small lobe is the primary site for interaction with MgATP. As seen in Figure 5, the density based on the difference map is consistent with the adenine moiety of the nucleotide oriented towards the base of the cleft beneath the β-sheet, with the phosphates facing outwards, towards the edge of the cleft. This structure is distinct from the Rossmann fold that is characteristic of many nucleotide binding proteins.

The larger lobe, in contrast, is remarkable for its predominance of helical structure. Seven helices are found in this C-terminal domain. A particularly unusual feature are the antiparallel hydrophobic helices, helix E (residues 140 through 159) and especially helix F (residues 218 through 233), that extend right through the core of this domain. The only region of β-structure in this lobe is located on the surface of the cleft at the interface between the two lobes where four antiparallel β-strands form a sheet. Most of the regions important for peptide recognition, as well as some conserved residues likely to be involved in catalysis, are located within this larger lobe.

The C-terminal 70 amino acids, residues 281 through 350, extend over a large portion of the surface of the enzyme from the bottom of the large lobe to the top of the small lobe. The part of this extended chain that passes through the region linking the two lobes appears to participate in recognition of both the peptide and the nucleotide, even though these amino acids are outside the conserved catalytic core. The other extended chain connecting the two lobes of the enzyme, residues 120 through 127, likewise, passes through this linker region between the small and large lobe and also participates in peptide recognition. Hence, this linking region consisting of both chains may contribute in part to the observed peptide-induced conformational changes described earlier. An overall two dimensional topology diagram for the C-subunit of cAPK is presented in Figure 6. Residues corresponding to the secondary structure elements are as follows: β-strands - 1:43-48, 2:57-63, 3:67-75, 4:106-111, 5:115-120, 6:1610164, 7:171-175, 8:178-183, 9:188-191; α-helices - A:15-31, B:76-82, C-84-97, D:-128-135, E:140-159, F:218-233, G-244-252, H:263-272, I:288-293. J:301-307.

CORRELATION OF STRUCTURAL DATA WITH CHEMICAL DATA

As discussed above, chemical data can be used to confirm the correct interpretation of the electron density map. Chemical analysis has been used as a way to obtain structural data in the absence of X-ray crystallography. Since the protein kinase family is an enzymatic group of major import, a significant body of chemical data is available. While this data cannot be used to predict a three-dimensional structure for affector modelling, it does provide a body of data that can be used to confirm and ensure the consistency of the three-dimensional structure. Thus, once a crystal structure is obtained for a model enzyme and its affector, the chemical data present in the literature can be used to examine the consistency of the model before proceeding to the design step. The three dimensional structure of the enzyme-affector complex should provide a solid explanation for the earlier chemical data. Information provided from chemical data together with structural data is used to obtain the both the template and the "lock" derived therefrom.

For example, evidence for localizing the nucleotide binding site near the amino-terminus first came from affinity labeling with an analogue of MgATP, fluorosulfonyl benzoyl adenosine (FSBA). Labeling with a hydrophobic carbodiimide, DCCD, identified two carboxyl groups near the MgATP binding site, Asp184 and Glu91, and, furthermore, established that Asp184 could be readily cross-linked to Lys72 in the apoenzyme. The structure of the binary complex without bound MgATP (Fig. 7) confirms that all three residues are localized in close proximity to one another, while the difference Fourier map with the ternary complex places these residues close to the γ-phosphate region of MgATP (see Fig. 5). Figure 7 provides stereo views of selected conserved areas. 1.5-σ ($2F_o$-F_c) electron density (10 to 2.7Å) is shown superimposed on the latest refined coordinates. In Figure 7A the sidechains of the invariant Lys72, Glu91, and Asp184 are shown in proximity to each other. Figure 7B shows the catalytic loop, Arg-Asp-Leu-Lys-Pro-Glu-Asn (165-171), together with part of PKI(5-24). Arg 20 of PKI(5-24) is labeled as 365. Lys72 is on β-strand 3, and Glu91 lies along the edge of the C-helix that faces the cleft. Asp184 is located on the loop connecting β-strands 8 and 9, and this loop also lines the cleft. All three residues are invariant in every protein kinase. Therefore these residues can be used as anchors for modeling the three dimensional structure of other protein kinases.

The MgATP binding site was defined more globally by differential labeling with acetic anhydride. By describing the reactivity of each lysine side-chain in the presence and absence of substrates, it was shown by Buechler et al., Biochemistry 28:3018-3024 (1989), that the specific protection afforded by MgATP was localized exclusively to residues in the

small lobe. In addition, to Lys72, MgATP protected Lys76 and Lys47 against modification by acetic anhydride. These protected lysines also flank the conserved glycine-rich loop that lies between β-strands 1 and 2. Based on the difference Fourier shown in Figure 5, this loop is close to the phosphates of MgATP.

Chemical studies using an affinity analogue have shown that Cys 199 is important for peptide binding. Modification of Cys 199 leads to loss of activity, and MgATP protects against inactivation. In contrast, Cys 343 can be covalently modified with no concomitant loss of activity. The structural analysis reported here indicates that Cys199 is on the surface of the cleft that interacts with the C-terminus of the inhibitor peptide, and Cys343 is on the surface of the small lobe. This distance measured between the two α-carbons of Cys199 and Cys343 in the crystal structure is 24Å. Thus, some of the chemical data is confirmed by the crystal structure.

CONSERVED REGIONS AND THEIR FUNCTIONS

The fact that all known protein kinases share a conserved catalytic core that is homologous to the C-subunit provides information that independently highlights important regions. This conserved catalytic core begins with the β-1 strand in the small lobe and extends through Arg280 in the large lobe (Hanks et al., supra) The two lobes comprising this conserved catalytic core can be seen clearly in Figure 8. Figure 8A is a space-filling model of the catalytic core (residues 40-280) shared by all protein kinases. The small lobe corresponding to the nucleotide binding fold 1 (residues (40-126); the larger lobe 2 (residues 127-280). In this model the bound peptide is not shown. Figure 8B is a diagram of the conserved catalytic core using the RIBBON program of the PAP package (J. P. Priestle, J. Appl. Cryst. 21:572, 1988 and available from the Molecular Simulation Laboratory at the University of Minnesota, Minneapolis, MN). Regions of the linear sequence noted by Hanks et al., supra, are indicated. The protein kinase having the largest insert at each position is designated using the following notation to define each insert: Gene/Protein Name: NH_2-terminal C-subunit residue no. (insert length) COOH-terminal C-subunit residue no. The inserts are CDC7:64(14)65, KIN1:83(26)84, PKC-γ:98(6)99, c-mos:113(5)114, PDGFR:137(99)138, CDC7:196(82)197, ran^{+1}:210(23)211, HSVK:240(11)241, CDC7:260(93)261, 7less:178(7)179. Figure 8C is identical to Figure 8A, but includes PKI(5-24) 3. Within this conserved core are nine invariant amino acids, as well as several highly conserved residues. Most of these conserved residues contribute directly to either MgATP binding or catalysis. Others, such as Arg280 and Asp208, exist as ion-pairs

and link two segments of the polypeptide chain that are widely separated in the linear sequence.

In addition, to providing information on conserved residues, sequence comparisons among protein kinases also identify inserts, sometimes quite sizable, that lie within the catalytic core. These inserts were noted by Hanks et al., supra, but their conformation in the overall structure of the catalytic subunit and their relationship to other regions of the catalytic core is described for the first time here. The locations of these inserts are indicated in Figure 8. All inserts invariably are located at loops on the surface of the protein and can be accommodated within the tertiary structure.

The structures of several important regions of the catalytic subunit are described below. Two highly conserved loops, as well as a triad of invariant charged residues, appear to be particularly important for nucleotide binding and catalysis. However the regions important for recognition of the peptide substrate are quite variable and were not available until the crystallized structure was analyzed. Predictions based on these variabilities are heretofore undescribed.

GLYCINE-RICH LOOP

The glycine-rich segment, Gly^{50}-Thr-Gly^{52}-Ser-Phe-Gly^{55}, was identified originally as part of the MgATP binding site based on its proximity to Lys72 and on differential labeling with acetic anhydride, since all of the lysines flanking this region, Lys47, Lys72, and Lys76, are protected in the presence of MgATP. The specific structural explanation obtained from crystallographic data for the protection of Lys47 is due to ionic pairing with the side chain of Glu333 while Lys76 ion-pairs with Glu346. Thus, conformation changes that occur around the glycine-rich loop as a consequence of MgATP and peptide binding are understood from the structural data in combination with known chemical data.

A glycine-rich motif is associated with many nucleotide binding sites, and this region has been the subject of much speculation and model building. The Rossmann fold, found in many nucleotide binding sites, contains a sheet of mostly parallel β-strands containing a glycine-rich loop. A similar motif containing a glycine-rich loop is found in other proteins such as adenylate kinase and p21 ras. The protein kinase fold found in the C-subunit and conserved in over one hundred protein kinases, does not conform to either of these motifs; it forms a unique nucleotide binding site. The uniqueness of this site is summarized as follows: (1) The glycine-rich segment lies at a sharp turn that joins two antiparallel strands at the beginning of the β-sheet. (2) The phosphate binding site is not dominated by a helix whose dipole points towards the phosphate. (3) The nucleotide does not lie along the edge

of the β-sheet. (4) An invariant Lys does not immediately follow this loop. Instead, the invariant Lys in the protein kinases, Lys72, is located in the β-3 strand and is a part of the stable scaffold of the structure. The single conserved element in each of these motifs is the glycine-rich loop whose apparent function is to serve as a phosphate anchor so that the γ-PO_4 is poised for transfer.

CATALYTIC LOOP

Another highly conserved loop in the C-subunit extends from Arg165 through Asn171 and can be termed the catalytic loop (Fig. 7B). This catalytic loop, Arg-Asp-Leu-Lys-Pro-Glu-Asn, contains 2 invariant residues, Asp166 and Asn171, and 2 highly conserved residues, Arg165 and Leu167. While the purpose of the glycine loop is to anchor the phosphate moiety and, in particular, to help position the γ-PO_4 so that it is poised for transfer, it is the catalytic loop that appears to be the central hub that communications to many different parts of the molecule. This loop not only directs the catalytic event, but also guides the peptide into its proper orientation so that catalysis can occur. The loop itself and, in particular, the residues that are important for catalysis are highly conserved, while the parts of the loop that direct the peptide binding are not.

Asp166 is one of 4 invariant carboxyl groups in the protein kinase family. It is the only one that is oriented towards the Ala side chain at the pseudo-phosphorylation site in the bound inhibitor peptide. Asp166 most likely functions as a catalytic base. Catalysis is thought to occur as a direct in-line transfer without an enzyme bound phospho-intermediate.

INTERDOMAIN CONTACTS:

The triad composed of the side chains of Lys72, Asp184, and Glu91, shown in Figure 7A, is conserved in every protein kinase and is close to the γ-PO_4 of MgATP. Asp184 was a candidate for the catalytic base; however, the structure indicates that a more plausible role is participation in the chelation of Mg^{2+} in the MgATP complex. The side chain of Asp 184 also comes within 4-5Å of the side chain of Asn171. This cluster, Asp184, Asn171, and Asp166, thus forms a second triad of invariant amino acids. Asp184, being a component of both triads, has the potential to shuttle between the two conserved loops, the glycine-rich loop in the small lobe and the catalytic loop in the larger lobe. Hence, if the position of Asp184 changes following the binding of MgATP, as it probably will given its location in the structure relative to the MgATP binding site, the consequences will have a direct impact on both conserved loops. If, for example, Asp184 participates in the chelation of Mg^{+2}, its negative charge would be sequestered from the catalytic loop, thus allowing the other

residues to rearrange in order to maximize the nucleophilicity of the serine hydroxyl moiety that is poised to receive the phosphate from ATP.

This is the first protein kinase structure to be reported. The protein kinases represent a large family of over 100 enzymes that includes growth factor receptors as well as many oncoproteins. In spite of the tremendous diversity of these enzymes, all share a conserved catalytic core that retains the same essential features of secondary and tertiary structure and the same general mechanism of catalysis. The essential hallmarks of this conserved core include: (1) two lobes with a cleft between that is occupied by the substrates, (2) a unique nucleotide binding fold dominated by β-structure, (3) a largely helical domain associated with peptide binding and catalysis, (4) two β-sheets converging at the active site near the domain interface, and (5) two conserved loops, one in each lobe, that converge at the active site. In marked contrast to these conserved features shared by all protein kinases, recognition of the peptide by the catalytic subunit involves non-conserved amino acids, and the peptide binding sites extend over diverse and widely separated regions on the surface of the enzyme. The detailed structure of the bound inhibitor peptide and its specific interactions with the catalytic subunit are described below.

Affector binding site data may incorporate information derived from several experimental avenues. In addition, to crystallographic studies, substrate analogues provide insights into the specific features of a given substrate that are important for recognition. Chemical approaches such as affinity labeling and group specific labeling can identify regions and specific residues that are in close proximity to substrates. Crystallographic studies can include a structural analysis of the apoenzyme, i.e. the structure of the enzyme without other associated molecules. However, more importantly, crystallographic studies of co-crystals of the enzyme with bound substrates or affectors are provided, so that the precise features of the active site can be defined.

Thus, in the model system of the present invention, crystals of the cAMP-dependent protein kinase C-subunit/PKI(5-24) were obtained and structural data derived therefrom. This structure of the catalytic subunit is presented as example 4. The inhibitor peptide PKI(5-24) is a fragment of the heat stable protein kinase inhibitor. Additional information about this inhibitor can be found in a publication by H.-C. Cheng et al. (Biochem J. 231:655-661, 1986). This peptide includes the consensus features common to all peptide substrates and inhibitors of cAMP-dependent protein kinase. In addition, it contains other features that convey unique high affinity binding. The crystals of complexed enzyme and inhibitor

provide insight into the guidelines necessary for designing affector molecules for other protein kinases.

The general requirements for peptide recognition by the catalytic subunit were characterized originally using synthetic peptides. These studies found a consensus sequence that includes two basic residues, typically arginines, followed by one intervening small residue preceding the site of phosphotransfer. The phosphate acceptor site, either Ser or Thr, is followed immediately by a large hydrophobic residue. The typical peptide substrate used for this kinase, based on the phosphorylation site in pyruvate kinase, is shown in Table 2. Replacement of the Ser with an Ala generates an inhibitor peptide with poor affinity. In contrast is the inhibitor peptide, PKI(5-24), derived from the thermostable protein kinase inhibitor (PKI). This peptide, seen in 2, encompasses the consensus sequences described above but also contains additional unique features that convey high affinity binding. The particular features that contribute to high affinity binding were defined using peptide analogues, and the most important ones are also indicated in 2. This peptide, PKI(5-24), was co-crystallized with the catalytic subunit, and the structure of that peptide as well as its interaction with the protein are discussed below.

A schematic of substrate and inhibitor peptides of cAMP-dependent protein kinase are provided in Table 2. The nomenclature used for the peptides designates the phosphorylation site or pseudophosphorylation site residue as P. In the case of substrates, P will be Ser or Thr; in the case of PKI(5-24), P is Ala. The residues flanking this site are designated as P+1, P-1, etc. as indicated. This nomenclature provides a common frame of reference for all peptide substrates and inhibitors and can be invoked readily for every protein kinase.

The Ser peptide is based on the *in vivo* phosphorylation site in pyruvate kinase. Residues shown to be important for peptide recognition are shaded and were identified using synthetic peptide analogues of the Ser peptide and of PKI. Procedures for determining which residues are important for peptide recognition using peptide analogues can be found in articles by Glass et al. and Kemp et al. (J. Biol. Chem. 262:8802-8810, 1989 and J. Biol. Chem. 252:4888-4894, 1977 respectively.)

Example 5

Conformation Determination of the Bound Inhibitor

The conformation of bound PKI(5-24) is shown in Figure 9. Backbone C and N atoms are shown in bold. Residues particularly important for binding are labelled according to the nomenclature of 2. The amino-terminus extending from the P-16 Thr through the P-8

Ala forms an amphipathic α-helix. This helix is followed by a turn flanked by glycines at the P-7 and P-4 positions. The glycines may be important for accommodating the turn or for providing flexibility to facilitate binding of the Arg that follows each Gly. The remainder of the peptide is in an extended conformation, and the density corresponding to the region at the C-terminus, the P+2 Asp and the P+3 His, is not well defined.

The catalytic subunit itself consists of 2 lobes - a smaller lobe, associated primarily with MgATP binding, and a larger lobe. Nearly all of the features necessary for peptide recognition are found within the larger lobe, although the specific residues involved are widely dispersed both in the linear sequence and on the surface of the enzyme. The extended portion of the peptide that includes the consensus region for recognition of all substrates and inhibitors lies along the surface of the cleft corresponding to the larger lobe. The helical segment of the peptide is amphipathic, and its hydrophobic side lies in a hydrophobic pocket on the surface of the large lobe. The specific interactions of the peptide with the protein can be described by (i) the interactions that account for the unique highly affinity binding of PKI and (ii) by the features of the protein that are important for recognizing the consensus sequence common to both the inhibitors and substrate.

HIGH AFFINITY BINDING SITE

Based on the crystal structure, the high affinity binding attributed to the N-terminus of PKI(5-24) is dominated by hydrophobic interactions involving primarily the phenylalanine side chain at the P-11 position. Glass et al. showed that a replacement of this Phe with an Ala caused a 100-fold increase in K_i while replacement with 1'-napthylalanine, a residue that is considerably larger and more hydrophobic than Phe, actually decreased the K_i by 4-fold. Figure 10 illustrates the high affinity binding site interactions. A hydrophobic pocket on the surface of the C-subunit nicely complements the hydrophobic face of the helix in the inhibitor peptide. This hydrophobic pocket is lined by residues 235 through 239, Tyr-Pro-Pro-Phe-Phe, with the phenyl ring in the inhibitor peptide sandwiched between the side chains of Tyr235 and Phe239. In Figure 10A the P-11 Phe ring (numbered 356) is shown in relation to three nearby hydrophobic residues of the C-subunit: Tyr 235, Pro 236, and Phe 239. Figure 10B illustrates the interactions of the P-11 Phe and P-6 Arg sidechains with the C-subunit. Distances between charged-residue sidechain atoms <3.5Å apart are indicated by thin connecting lines. Based on the structure, the Tyr at the P-14 position is not essential for this hydrophobic interaction. In addition, to the hydrophobic interactions associated with the helix, the orientation of the high affinity binding region PKI(5-24) is fixed by the ionic

contacts involving the P-6 Arg. Two nitrogens in the guanidine side chain of this Arg undergo ion-pairing with the two oxygens of the carboxyl group of Glu203.

CONSENSUS RECOGNITION SITE

Figure 11 summarizes the interactions that contribute to recognition of the common consensus region of the inhibitor peptide. The interactions of the P-3 and P-2 Arg residues and the P+1 Ile residue with C-subunit residues are shown. Lines are drawn between charged-residue sidechain atoms <3.5Å apart. The P+1 Ile sidechain projects into the hydrophobic area formed by Leu 198, Pro 202, and Leu 205. Electrostatic interactions dominate the portion of the peptide proximal to the site of phosphotransfer, while hydrophobic interactions dominate the C-terminal region distal to the phosphotransfer site.

Two important requirements for peptide recognition by cAPK are basic residues at the P-3 and P-2 positions. Others have shown that replacing either Arg in the Ser peptide substrate leads to a 16-400-fold increase in K_m, even when the Arg is replaced with a Lys. The environment flanking the P-3 and P-2 arginines explains these results since each Arg interacts with more than one carboxyl side chain.

Table 3 provides a listing of the amino acid residues present at the various points of contact between PKI(5-24) and two protein kinases, cAPK and casein kinase II (CKII). It can be seen from Figure 11 and Table 3 that in the C subunit of cAPK, that those residues lining the p+1 site are very hydrophobic and provide a pocket for the hydrophobic p+1 residues. In CKII, the residues lining this pocket are all basic or positively charged. This basic pocket compliments an acidic residue at the p+1 position and this is consistent with the known specificity of CKII, i.e. CKII prefers acidic groups at the p+1 position.

Figure 12 provides information on the consensus recognition site binding interactions. The electron density corresponding to the anionic P-3 site is shown in Figure 12A. Residue numbers 361, 364, 365, and 368 correspond respectively to PKI(5-24) P-6, P-3, P-2, and P+1 residues. The electron density of the P-3 Arg sidechain tip is shown in proximity to Thr 51 carbonyl in the glycine-rich loop, and Glu 127 and Glu 331 sidechain carboxylates of the domain-linking region. In Figure 12B the 1-σ ($2F_o$-F_c) electron density of the P-2 Arg sidechain is shown in proximity to sidechain carboxylates of Glu 170 of the catalytic loop and Glu 230; the P-6 Arg sidechain is shown near sidechain carboxylate of Glu 203. In Figure 12C the 1.5-σ ($2F_oF_c$) electron density of the P+1 Ile sidechain is shown projecting into a hydrophobic pocket comprised of residues Leu198, Pro202, and Leu205. The side chain of this P-3 Arg interacts with Glu127. The carboxyl side chain of Glu331 also is approximately 3Å from the guanidinium nitrogens. The tip of Asp329 is approximately

5Å away. Thus, the position of the guanidinium moiety is fixed. In addition, the side chain of the P-3 Arg comes close to the backbone carbonyl of Thr51 in the glycine-rich loop and to the hydroxyls of the ribose ring. The side chain of Glu333 lies close to Lys47 in β-strand 1, and the side chain Glu334 is approximately 3Å from the hydroxyl group of Thr48.

The P-2 site is also very anionic, and this Arg, likewise, interacts with more than one carboxyl group. As indicated in Figures 11 and 12B, the ε-nitrogen forms an ion-pair with Glu170, while one of the terminal nitrogens interacts with Glu230. Glu 203 also comes close to this guanidinium side chain; however, its interaction with the P-6 Arg is dominant. In the absence of an Arg at the P-6 position, Glu230 may ion-pair with the P-2 Arg. Unlike the P-3 recognition site, all of the carboxyl groups at the P-2 site are an integral part of the large lobe.

DISTAL HYDROPHOBIC SITE (P+1)

Peptide analogue studies of others predicted a hydrophobic requirement at the P+1 position since replacement of the Leu with Gly in PKI(5-24) caused a 150-fold increase in K_m. The reasons for this requirement are now clear from the structure (Figs. 11 and 12C). Leu198, Pro202, and Leu205 form a hydrophobic groove that surrounds the Ile side chain. This hydrophobic region that constitutes the P+1 site lies at the edge of the cleft and is likely important for proper orientation of the actual site of phosphotransfer at the P position. In the binary complex this region begins to align in an antiparallel β-like configuration with the carbonyl of the P+1 Ile coming less than 4Å from the backbone amide of Gly200 and the carbonyl of Gly200 coming within approximately 3Å of the backbone amide of this Ile at the P+1 position (Fig. 13B). Substitution of a Pro for Leu at the P+1 position in the Ser peptide (2) yields an extremely poor substrate. Nevertheless, a depsipeptide analogue of this peptide lacking an amide proton at this P+1 site is still a good substrate for the catalytic subunit.

Figure 13 illustrates the catalytic site area. Residue numbers 364 and 367 correspond to the P-3 Arg and the P Ala. 1.5-σ ($2F_o$-F_c) electron density is shown in all cases. Figure 13A provides the site of catalysis together with the possible catalytic base sidechain of Asp 166 near the β-C of the P Ala. Thr 51 of the glycine-rich loop is shown near the P-3 Arg sidechain, and hydrophobic sidechains of residues Phe 54 (at the loop apex) and Phe 187 are shown near the site of phosphotransfer. The addition of a hydroxyl group would place the side chain of the residue at the P position close enough for a direct transfer of the γ-phosphate for MgATP. The side chain of the P-1 Asn also interacts with the glycine-rich loop as shown in Fig. 13A. Figure 13B diagrams the consensus recognition

site residues Arg-Arg-Asn-Ala-Ile together with the glycine-rich phosphate anchor loop to the left and residues 198-202 to the right. The term "residue" is here used interchangeably with amino acid. The carbonyl of Gly 200 can be seen pointing to the amide N of the P+1 Ile. Figure 13C shows the phosphate of Thr 197 buried among sidechains of cationic and H-bonding residues (His 87, Arg 165, Lys 189, Thr 195). Cys 199 is also shown nearby.

Thr197, one of the two stable phosphorylation sites in this enzyme, also flanks the P+1 site. Multiple electrostatic interactions, seen in Figure 13C, hold this PO_4 in place and account for its resistance to removal by phosphatases. Fixing this phosphate moiety contributes conformational stability, not only to Thr197 but also to the adjacent hydrophobic residues important for recognition at the P+1 site and for the proper orientation of the site of phosphotransfer. Based on the crystal structure, this anionic group appears to be important for the final correct assembly of the structure.

CORRELATION WITH EXPERIMENTAL PREDICTIONS

Several chemical approaches identified amino acid side chains that contribute to peptide recognition. Differential labeling with a water soluble carbodiimide, 1-ethyl-3(3-dimethylaminopropyl) carbodiimide (EDC), targeted solvent-accessible carboxyl groups that were accessible in the free C-subunit but protected in the presence of substrate (Buechler et al. Biochemistry 29:1937-1943, 1990). Two regions were identified using this approach. Glu170 was very reactive in the absence of peptide, but fully protected in the presence of peptide. The other region was the cluster of carboxyl groups near the C-terminus, Asp^{328}-Asp-Tyr-Glu-Glu-Glu-Glu^{334}. As indicated in Figure 12, Glu170 interacts with the P-2 Arg while the cluster of carboxyl groups flanks the P-3 site.

The crystal structure localized Cys199 close to the peptide recognition site and to the γ-PO_4 subsite of ATP. In the binary complex, Cys 199 does not appear to participate in peptide binding other than to contribute to the general hydrophobic environment around the P+1 site.

CONFORMATIONAL CHANGES ASSOCIATED WITH PEPTIDE BINDING

Substrate-induced conformational changes are associated with peptide binding to the catalytic subunit. Global changes in conformation, first observed using circular dichroism, showed both a loss of alpha-helical content and an increase in beta structure following peptide binding. A global change in shape also was observed using low angle neutron scattering. These results demonstrated a reduction of the radius of gyration (Rg) following substrate binding and furthermore established that the inhibitor peptide alone, but not MgATP, was sufficient to cause the reduction in Rg. The substrate-induced reduction in Rg

indicates that the apoenzyme corresponds to an open configuration of the protein while the binary and ternary complex represent a closed configuration.

The recognition of the peptide by the catalytic subunit is believed to be a multistep process. The initial step, associated with a loss in α-helical structure, was induced by both the substrate and inhibitor heptapeptides shown in 2. The second step, presumably corresponding to the final orientation of the peptide into the correct position at the active site, was associated with an increase in β-structure and could only be accomplished with the substrate peptide, not by the Ala peptide inhibitor. This increase in β-structure is probably due, in part, to the P+1 region of the peptide interacting the protein. Understanding these substrate-induced conformational changes will eventually require a detailed comparison of the apoenzyme structure with binary and ternary complexes containing inhibitors and substrate peptides both in the presence and absence of MgATP.

The peptide-induced conformational changes in catalytic subunit may reflect a closing of the cleft and probably involve the region linking the small and large lobes as well. This linker region consists of two chains: residues 123 through 127 and a highly acidic segment, residues 328-334. The P-3 peptide binding site is the only region of the inhibitor peptide that interacts directly with both of these extended chains that link the two lobes. One anionic group at the P-3 site is Glu127 and the other is Glu331. Since several of the carboxy groups in the C-terminal linking chain also interact with portions of the nucleotide binding site, even in the binary complex, this P-3 residue may contribute to the substrate-induced conformational changes.

CONSERVED AND VARIABLE SITES IN PROTEIN KINASES

The recognition of a protein substrate by the catalytic subunit is not unlike the recognition of a protein antigen by the variable domain of an immunoglobulin. The binding sites of both structures are dominated by interfacing β-sheets surrounded by loops that participate in recognition of the protein. The catalytic subunit also has helical regions, but it is the β-sheets that converge at the active site and it is the loops that play the dominant role in peptide recognition and catalysis. One β-sheet comes from the small lobe and the other from the large lobe. These two sheets are sandwiched together at the cleft. In the case of protein kinases, two of the loops are essential for catalysis and are highly conserved, unlike the immunoglobulins, whose function is only to bind antigens.

The two essential conserved loops that assemble at the site of catalysis in the catalytic subunit, seen in Figures 14 and 15, are the glycine-rich loop in the small lobe and the catalytic loop in the large lobe. Both lie on the surface that lines the cleft between the

two lobes. The glycine-rich loop serves as an anchor for the phosphates of MgATP, whereas the catalytic loop is essential for peptide binding and catalysis. Key features of the active site of the catalytic subunit are shown in Figure 14. Nine of the amino acids that are nearly invariant in all protein kinases are indicated. Gly186, another invariant residue, is not shown. The alpha carbons are in black, oxygens dotted, and nitrogens in horizontal hatching. The position of the phosphorylation site at Thr197 is indicated by vertical hatching. The portion of the active site associated with the small lobe is shaded and includes three of the invariant amino acids, Gly 52, Lys72, and Glu91. The remaining six are located in the large lobe. Residues close enough for hydrogen bonding or ion pairing are indicated by a dashed line while residues within 4-5 Å of one another are connected by a dotted line. As seen in Figure 14, seven of the nine invariant amino acids conserved in all protein kinases are located here, either in the loops themselves or connecting directly with loop residues. The single invariant glycine, Gly52, lies in the phosphate anchoring loop. The proposed catalytic base, Asp166, as well as Asn171, are in the catalytic loop. It is remarkable how thoroughly interconnected this region is with multiple ion pairs providing a finely tuned scaffolding for communication at the active site.

The three invariant residues in the small lobe all participate in nucleotide binding. Unlike Gly52, which is part of a flexible loop, both Lys72 and Glu91 are anchored to defined parts of the secondary structure - Lys72 to β-strand 3 and Glu91 to the C-helix. The difference Fourier map shows the phosphate density near these residues, with the presumed γ-PO_4 density close enough to the P Ala C_β for phosphotransfer were it a Ser[Thr] and indicates that these residues play a key role in the recognition of the phosphates of MgATP.

In the catalytic loop the two invariant residues, Asp166 and Asn171, interact with each other. Not only are their side chains close, but, more importantly, the nitrogen in the amide side chain of Asn171 is less than 3Å from the backbone carbonyl of Asp166. One additional nearly invariant residue, Asp220, contributes directly to stabilization of the catalytic loop. The two oxygens of this carboxylate come with hydrogen bonding distance of the backbone carbonyl and amide of residue 164 that immediately precedes the loop. The interaction of the catalytic loop with a conserved residue that lies deep within the large lobe fixes the loop from one side while peptide binding and interactions with the small lobe fix it from the opposite direction. As seen in Figure 13A and 13B, the consensus region of the peptide is sandwiched between the P+1 site on one side and the glycine-rich loop on the other side.

Of all the invariant residues, Asp184 is the only one that appears to communicate with both the small lobe and the large lobe. In the binary complex, it is most closely associated with Lys72, but it is also only 4-5Å from Asn171 and Asp166 in the catalytic loop. Although not shown in Figure 14, Asp184 is itself part of a tight turn with the carboxylate located within hydrogen bonding distance of the backbone amide of Gly186, another invariant residue. This entire segment, Asp166-Phe-Gly, is highly conserved in all protein kinases, and hydrogen bonding to stabilize the turn is probably conserved as well. Asp184 certainly has the potential to shuttle between the two conserved loops, and it is anticipated that the contacts of Asp184 will differ somewhat in both the apoenzyme and in the ternary complex containing bound MgATP as well as peptide. If Asp184 participates in the chelation of Mg^{2+}, as disclosed above, then this charge will be sequestered from the immediate environment of the catalytic loop. Other residues close to the conserved residues in the catalytic loop in the binary complex are Tyr164 and Lys 168. The Tyr 164 side chain is less than 3Å from the side chain nitrogen of Asn171, and the Lys168 side chain comes close to the carboxylate of Asp166. Either Tyr or His, another good hydrogen-bonding residue, is always found at position 164, so this contact can also be conserved. Any significant change in the position of Asp184 will likely change the environment of the catalytic loop. Asp184, as well as Asn171 and Asp166, have also been identified as a sequence motif associated with many phosphotransferases, and this may represent a common mechanism among protein kinases.

The versatility and importance of the catalytic loop is highlighted not only by the conserved networking of essential amino acids at the active site, but also by the special ways in which this conserved network communicates with the variable residues that compose the peptide binding sites. This communication specifically involves loop residues that are not highly conserved. Glu170, for example, contributes directly to the anionic P-2 site. Thr201 in the P+1 site, on the other hand, comes very close to the side chain of Asp166. These two particular regions of contact involving the peptide binding site and the catalytic loop, Lys^{168}-Pro-Glu and Thr^{201}-Pro-Glu-Tyr-Leu-Ala-Pro-Glu, contain sequences that differ characteristically between the kinases that transfer phosphate to Ser/Thr and those that transfer phosphate to tyrosine (Hanks et al., supra).

Arg165 is actually highly conserved in most protein kinases, and it connects in a unique way with the P+1 peptide binding site. Specifically, it points towards the phosphothreonine and helps to fix that phosphate so that the hydrophobic groove that follows and provides a pocket for the side chain of the P+1 residue is firmly positioned

(Figure 13C). This is an autophosphorylation site, and it is the only phosphorylation site in the catalytic subunit that could conceivably result from an intramolecular autophosphorylation. Chemical analysis has shown that this phosphate is very resistant to removal by phosphatases and based on this crystallographic data, appears to contribute to the final conformation stability of the enzyme. It should be emphasized as well that a phosphorylation site in this region of the protein is not a conserved feature of all protein kinases. Some kinases such as $pp60^{c\text{-}src}$, a protooncogene whose viral counterpart is found in Rous Sarcoma Virus, do have an autophosphorylation site nearby, but many others do not. Whether the catalytic loop communicates in unique ways with other autophosphorylation sites in other protein kinases remains to be established.

The two invariant residues that are most distant from the active site are Asp208 and Arg280. These residues constitute a conserved ion pair that lies just beneath the P+1 site and appears to stabilize a very hydrophobic region that buttresses the P+1 peptide binding site.

Figure 15 is a schematic of the conserved and variable regions of the catalytic subunit. The ribbon diagram depicts the folding of the catalytic subunit. Conserved regions include two loops - the glycine-rich loop and the catalytic loop - and are indicated. The variable peptide binding sites are shown as solid areas. Invariant amino acids Gly52, Lys72, Glu91, Asp166, Asn171, Asp184, Glu208, Asp220, and Arg280 are indicated by a large dot and are numbered. Dashed lines indicate residues that are close enough to pair, while the dotted line extends from Arg165 to the Thr197. Several points should be emphasized regarding the recognition of a peptide or protein substrate by the catalytic subunit. First is the number of sites and their diversity. Some of these peripheral peptide recognition sites are hydrophilic and highly charged; others are hydrophobic. As seen in Figure 15, most are found within the large lobe of the catalytic core shared by all protein kinases, but some also lie outside of this boundary. A second observation is that the requirements for recognition at the consensus site are not absolute. A comparison of *in vivo* phosphorylation sites reveals that the actual residues at each site vary somewhat as does the spacing between the positively charge side chains and the site of phosphotransfer. Thus, even in the consensus region, some variability can be tolerated. A third point is the potential for variability in recognition of different inhibitor, and presumably substrate, proteins that bind with a high affinity to the catalytic subunit. Most of the features essential for the high affinity recognition of PKI are apparent from this structure of the binary complex. The regulatory subunit, however, also binds to the C-subunit with a subnanomolar affinity in the absence

of cAMP. The consensus region, P-3 through P+1, is shared by both molecules. However, the R-subunit, cleaved at the P-5 position, still retains is high affinity binding for the C-subunit. In addition, the P-16 to P+1 region of the R^I-subunit is Pro-Pro-Pro-Pro-Asn-Pro-Val-Val-Lys-Gly-Arg-Arg-Arg-Arg-Gly-Ala-Ile, and this certainly cannot conform to the helical motif that dominates the corresponding region of PKI(5-24). Hence, an amphipathic helix is not required for the high affinity binding of the regulatory subunit. Instead, the residues that contribute to the high affinity binding of the regulatory subunit, specifically, must lie beyond the P+3 position and may complement a different portion of the surface of the C-subunit. This variability presumably can also extend to protein substrates where the catalytic subunit may recognize unique sequences that lie outside the consensus site.

Unlike the conserved residues that are invariant in all protein kinases, the sites involved in peptide recognition differ for each kinase. About 30% have some general similarities to cAPK. Others are quite different. However the template allows us to predict the specificity of each contact point. Figure 16 provides the sequence of PKI(5-24) and illustrates the distances between the points of contact and the catalytic site in three-dimensional space as measured from the template. The P site or site of catalysis is denoted by an arrow. Asterisks designate sites particularly important for the high affinity binding of PKI(5-24). Recognition sites essential for PKI binding to other substrates are denoted as labelled archways p+1, p-2, p-3, p-6, and p-11. All of the distances, with the exception of the p+1 site, are greater than 5 Å. That positions 5 Å or greater from the site of catalysis are important for inhibitor specificity have heretofore been undisclosed.

The identification of the subsites that are important to maintaining the specificity of the affector molecule interaction and provide Kd less than 100nM facilitates the design of other inhibitors. PKI(5-24) can be used as a scaffold for molding new inhibitors, and in addition once the electrochemical interactions are understood from an analysis of the three dimensional template, other affectors that are not peptides can additionally be identified. Thus, affectors could come from a group including but not necessarily limited to peptides, polypeptides, unmodified molecules existing in nature, synthetic molecules, nucleic acids, polymers, organics, or hydrocarbons. Molecules that exist in nature and that are known to interact with enzymes could be modified to produce affector molecules. Examples from this group include antibodies, antibiotics, protein, other enzymes, lipids, polysaccharides, saccharides and vitamins. Thus, inhibitors can be designed that utilize both conserved and nonconserved points of contact.

The invariant residues within the protein kinase family and specifically, cAPK, are used to apply the template and its coordinates to other protein kinases. There are 8-9 invariant residues for the protein kinase family. Other families may have differing numbers of invariant residues. Table 4 list the invariant residues and the distances between these resides. The distances are calculated between α-carbons. The distances between residues 52, 72 and 91 are expected to remain close to constant since these residues are all in the amino-terminal domain of the protein. Similarly, the distances between residues 166, 171, 184, 186, 208 and 280 would be expected to remain constant due to their being in the carboxy-terminal domain. Motion of the amino-terminal domain relative to the carboxy terminal domain is expected to change the distances between residues in different domains.

The distances calculated in Table 4 help form the model template since these three-dimensional positions are taken from the crystal diffraction patterns and help to define a conserved shape for the protein kinase family catalytic core. A point of contact is defined herein to occur at the invariant residues and is additionally defined as a point of close spatial approximation between the atoms of the residues within or around the catalytic core and the atoms of the affector. These points of contact affect the specificity and the Kd of the enzyme/affector interaction.

The template is best described by Figure 11. The coordinates for the template listed in Table 4 and Figure 17 provide the spatial characteristics that permit one of skill in the art to input the template structure into a computer program and perform the invention disclosed herein. While the coordinates together define a three-dimensional surface that permits visualization of the catalytic site, there are invariant residues that establish important foci within the structure.

Lys 72 is invariable within the catalytic site for the protein kinase family and is an anchor for superimposing other protein kinases onto the template. Asp 166 can additionally be a second important anchor. Similarly the other invariant positions likewise have importance for fitting other kinases. A combination of the coordinates with the invariant residue positions allows important regions within and around the catalytic site to be visualized. From a study of the interaction of cAPK with PKI(5-24), important hydrophobic and ionic interactions can be analyzed. When a new enzyme is superimposed onto these coordinates these hydrophobic and ionic interactions are assessed with PKI(5-24). It is then possible to study what changes can be made to PKI(5-24) to model a new affector. A study of the residue sidechains and the charge distribution within the site is used to fine tune the new affector.

Any protein kinase having homology in and around the catalytic site with cAPK can be used to design specific affector molecules. Hanks et al. provides a list with homologous residues highlighted. Many growth factor receptors have protein kinase activities. These include but are not limited to platelet-derived growth factor, colony stimulating factor, the insulin receptor family and epidermal growth factor. Protein kinases are involved in hematopoiesis and lymphopoiesis. Some, like myosin light chain kinase, are calcium-calmodulin dependent, and further, a variety of protein kinases are oncogenic products. These include but are not limited to viral and cellular homologues of src, mos, abl, Neu, Fgr, and Yes. Any of these kinases as well as others fitting the characteristics disclosed herein could be used in this invention to produce specific affector molecules.

The phosphorylation target sequences are available for a variety of protein kinases. These include phosphorylatable amino acids with their surrounding residues. For some kinases this will provide a good starting point for inhibitor design. Other protein kinases have a regulatory subunit associated with the catalytic subunit in the inactive form. The binding sequences with the regulatory subunits are other starting points for affector molecule design. Additionally, there are a group of protein kinases that have a regulatory domain. This domain binds the catalytic site when the enzyme is inactive. Binding of an exogenous molecule changes the kinase conformation such that the regulatory domain no longer binds. A review by Pearson et al. provides a table of protein kinase phosphorylation site sequences (Methods in Enzymology Vol. 200, 1991 in press).

Once a template is created there are several options available for designing an affector molecule and these were outlined in the section above entitled "Brief Description of Affector Design."

EXAMPLE 6

Inhibitor design for $pp60^{c\text{-}src}$ without $pp60^{c\text{-}src}$ purification

$pp60^{c\text{-}src}$ is the proto-oncogene homologue of the src protein kinase from Rous Sarcoma Virus. The protein causes unrestrained cell proliferation. In this example, the invariant residues for $pp60^{c\text{-}src}$ are identified with a star and in bold below:

```
        *       *       *
ESLRLEVKLGQGCFGEVWMGTWNGTTRVAIKTLKPGTMSPEAFLQEAQVMKKL
RHEKLV

QLYAVVSEEPIYIVTEYMSKGSLLDFLKGETGKYLRLPQLVDMAAQIASGMAYBE
RMNY
  *   *       *       *
```

VHRDLRAANILVGENLVCKVADFGLARLIEDNEYTARQGAKFPIKWTAPEAALY GRFTI

KSDVWSFGILLTELTTKGRVPYPGMVNREVLDQVERGYRMPCPPECPESLHDLH CQCWR

*

KEPEERPTFEYLQAFLEDYFTST

These residues are incorporated into the appropriate position from the invariant residues listed in Table 4 using the coordinate set provided in Figure 17. Once the template is in place and the catalytic site from $pp60^{c\text{-}src}$ has been superimposed onto the template, it is possible to visualize the catalytic site. The site can additionally be refined using the complementary target phosphorylation site for $pp60^{c\text{-}src}$.

RLIEDNEY*TARQGAK

* denotes the site of phosphorylation.

Residues are altered using computer modelling until a fit is achieved for $pp60^{c\text{-}src}$ on the template. Thus, residues 184, 166, 172, 220, 208, and 280 from the pp60 c-src sequence have positions in space that maintain those distances disclosed in Table 4. Ionic and hydrophobic amino acid side chains are matched within the catalytic core with complementary residues to create a new inhibitor molecule. Recombinant cAPK is then mutated to duplicate the three-dimensional structure within the core. Crystals of mutated cAPK are analyzed alone or together with a proposed inhibitor. The structure is again analyzed in the context of the invariant residues listed in Table 4.

Positions 52, 72, and 91 are mobile invariant residues whose positions will vary depending on the quality of inhibitor. The distances of these residues are listed in Table 4 for PKI(5-24) and cAPK. It is anticipated that peptide inhibitors of equal affinity for cAPK will have similar distances. Non-peptide inhibitors can be designed that do not produce a rotation, or fraction of fit, exactly in the same direction as peptide inhibitors, such as PKI(5-24). A comparison of the crystal structure of cAPK and cAPK with PKI(5-24) indicate that positions 52, 72 and 91 rotate 12° toward residues 184, 166, 172, 220, 208 and 280. This rotation defines a range of peptide inhibitors. Another strong peptide inhibitor will similarly produce a 12° rotation toward the six residues listed above while residues 52, 72 and 91 may have a smaller angle of rotation for weaker peptide inhibitors.

In addition, there are important points of contact between cAPK and PKI(5-24). The specific contact amino acids on PKI(5-24) are starred and the corresponding points of contact within the catalytic core of cAPK are identified as positions p+1, p-2, p-3, p-6 and p-11. These points of contact are conserved within the catalytic core of all protein kinases

and similar points of contact will be readily identifiable to those of skill in the art for other protein kinases. A sphere of influence having a radius of 11Å or less, more preferably 6Å or less, and extending from the inhibitor around the points of contact at positions p+1, p-2, p-3, p-6, and p-11 can be used to define regions that are critical for inhibitor specificity.

As described above, in connection with Figure 11, the points of contact can be used to identify the replacements necessary to design appropriate inhibitors or other affectors for a new enzyme. Thus, amino acid replacements are used which form appropriate ionic and hydrophobic interactions at these points of contact. Hydrogen bonding interactions are also preferably used to identify replacements. Of course, the modelling can extend beyond the identified points of contacts in order to provide still further specificity

This same type of analysis can be performed with the mutated cAPK that mimics the catalytic core of $pp60^{c\text{-}src}$. Thus, an analysis of the mutant crystals permits one to predict the affinity of a given inhibitor. The inhibitor can be further modified to improve the ionic and hydrophobic interactions surrounding the points of contact using the spheres of influence described above. The angle of rotation of the mobile invariant residues can be used to predict whether or not a given peptide inhibitor will be useful. These changes are all performed within the constraints of the coordinates of Figure 17.

A peptide inhibitor that, once modelled has distances similar to Table 4 and meets the design criteria described above can be synthesized and tested for function *in vitro* or *in vivo*.

The coordinates obtained from the binary complex and the resulting template allow us for the first time to fully appreciate the complexity and sophistication of the process by which a protein kinase recognizes its protein substrate. While peptide analogues provide important clues, the diversity of the peptide binding sites and their dispersion over such a wide area on the enzyme surface makes it imperative to have structural data on complexes of the enzyme with affector molecules. The structure of the binary complex of cAPK with PKI(5-24) provides, for the first time, a molecular basis for the rational design of affector molecules, both peptide and nonpeptide, that can target specific protein kinases. Furthermore, because the basic catalytic core of this enzyme is so conserved in all protein kinases, a template based on the crystal structure can also serve as a mold for modelling for other protein kinases.

Although this invention has been described using protein kinases as a model system, with cAPK being shown as a specific example of an enzyme for determining the template, the present invention is not intended to be limited to this model. Other changes to the

methods described herein will suggest themselves to those of ordinary skill in the art. Accordingly, the spirit and scope of the present invention is to be determined with reference to the appendant claims.

WE CLAIM:

1. A method of designing a highly specific affector which exerts an effect on the activity of a first enzyme, said first enzyme being a member of a class of enzymes having a conserved catalytic core, comprising:

identifying a second enzyme that is a member of said class in which a first affector can affect the activity of said second enzyme;

forming a first complex of said first affector and said second enzyme;

obtaining data regarding the conformation of said second enzyme at sites greater than 5 Å from the site of catalysis of said second enzyme in said first complex;

designing an affector which induces a conformation on said first enzyme at sites greater than 5 Å from the site of catalysis thereof which is homologous to the conformation of the conformation of said second enzyme at homologous sites in said first complex, when said affector is formed as a second complex with said first enzyme; and

producing said affector.

2. The method of Claim 1, additionally comprising crystallizing said first complex and obtaining X-ray crystallography data therefrom.

3. The method of Claim 1, wherein the designing step comprises:

identifying a potential affector likely to induce a conformation on the catalytic core of said first enzyme which is homologous to the conformation of the catalytic core of said second enzyme in said first complex, when said affector is formed as a second complex with said first enzyme; and

determining whether said potential affector induces said conformation through the use of a technique selected from the group consisting of computer modelling, small angle neutron scattering, and circular dichroism.

4. The method of Claim 3, wherein said potential affector comprises a peptide.

5. The method of Claim 3, wherein said potential affector comprises a molecule selected from the group consisting of nucleotides, polynucleotides, alcohols, polymers, lipids carbohydrates, sugars, native or synthetic molecules, protein and organic compounds and combinations thereof.

6. The method of Claim 1, wherein all of the members of said class have related functions.

7. The method of Claim 1, wherein the catalytic cores of all of the members of said class have conserved amino acid residues.

8. The method of Claim 7, wherein the designing step comprises designing an affector having homologous topography and charge fields that complement the catalytic core of said first enzyme and capable of inducing a conformation wherein the conserved amino acid residues of said first enzyme are in homologous locations to said second enzyme in said first complex.

9. The method of Claim 1, wherein each of the affectors is an inhibitor.

10. The method of Claims 1, wherein each of the affectors is an activator.

11. The method of Claim 1, wherein said first affector comprises all or a portion of said first enzyme.

12. The method of Claim 1, wherein said first complex is a holoenzyme.

13. The affector produced by the method of Claim 1.

14. The method of Claim 7, wherein said class of enzymes comprises protein kinases.

15. The method of Claim 14, wherein said second enzyme is a viral oncogene product or a cellular homologue thereof.

16. The method of Claim 15, wherein said second enzyme is p60 v-Src from RSV or its cellular homologue, pp60 c-src.

17. The method of Claim 16, wherein said second enzyme comprises cAMP-dependent protein kinase.

18. The method of Claim 2, wherein said second enzyme comprises a native mammalian protein kinase.

19. The method of Claim 2, wherein said second enzyme comprises recombinant protein kinase.

20. A method of designing a highly specific affector which exerts an effect on the activity of a first enzyme, said first enzyme being a member of a class of enzymes having conserved residues at an affector binding site, comprising:

identifying a second enzyme that is a member of said class in which a first affector can affect the activity of said second enzyme, said first affector having a dissociation constant with said second enzyme of less than 1 μM;

forming a first complex of said first affector and said second enzyme;

obtaining data regarding the conformation of the affector binding site of said second enzyme in said first complex;

designing an affector which induces a conformation on the affector binding site of said first enzyme which is homologous to the conformation of the affector binding site of said second enzyme in said first complex, when said affector is formed as a second complex with said first enzyme; and

producing said affector.

21. The method of Claim 20, wherein said class of enzymes have a nucleotide binding site and each of said affectors is capable of binding to said nucleotide binding site.

22. A method of designing a highly specific affector which exerts an effect on the activity of a first enzyme, said first enzyme being a member of a class of enzymes having a conserved catalytic core, comprising:

identifying a second enzyme that is a member of said class in which a first affector can affect the activity of said second enzyme;

forming a first complex of said first affector and said second enzyme, said first complex having at least three points of contact between said first affector and second enzyme;

obtaining data regarding the conformation of the catalytic core of said second enzyme in said first complex;

designing an affector which induces a conformation on the catalytic core of said first enzyme which is homologous to the conformation of the catalytic core of said second enzyme in said first complex, when said affector is formed as a second complex with said first enzyme; and

producing said affector

23. A crystallized protein kinase/affector complex having stable decay characteristics over 15 minutes.

24. A crystallized protein kinase/affector complex having a Bragg spacing diffraction limit of less than 4Å.

25. The crystallized protein kinase of Claim 24 having stable decay characteristics over 15 minutes.

26. A crystallized complex of a cAMP-dependent protein kinase and an inhibitor thereof.

27. Use of the crystallized complex of Claim 26 in an X-ray crystallography procedure to produce data regarding the three dimensional structure of said cAMP-dependent protein kinase in said complex.

28. Use of the data produced by Claim 27 for designing an inhibitor of a second protein kinase which will induce a similar three dimensional structure on the active site of said second protein kinase as the three dimensional structure of said cAMP-dependent protein kinase in said complex.

29. An inhibitor designed by Claim 28.

30. A method of preparing a highly specific affector of a first enzyme, said first enzyme being a member of a class of enzymes having a conserved catalytic core with a plurality of invariant residues, comprising:

a. identifying a second enzyme that is a member of said class and having a known affector thereof;

b. forming a first complex of said second enzyme and said known affector;

c. obtaining data regarding the three dimensional coordinates of said invariant residues in said first complex, said coordinates forming a template;

d. generating a model wherein said first enzyme is in a conformation in which said invariant residues are in substantially the same conformation as in said template;

e. identifying a change in the variable residues in the catalytic core of said first enzyme in the conformation of step (d) when compared to the variable residues in the catalytic core of said second enzyme in the conformation of step (b);

f. preparing a modified form of said second enzyme, wherein the modified second enzyme includes the non-conserved change identified in step (e);

g. designing an affector which computer modelling indicates will induce a conformation on the catalytic core of said first enzyme in which said invariant residues are in substantially the same coordinates as the coordinates of said template, when said first enzyme is formed as a second complex with the affector designed in this step; and

h. producing said affector.

31. The method of Claim 30 wherein said change is a non-conserved change in the variable residues.

32. The method of Claim 30, additionally comprising:

i. forming a third complex of said modified second enzyme and an affector capable of binding thereto;

j. obtaining data regarding the three dimensional coordinates of the invariant residues in said third complex; and

k. using the data obtained in step (i) to design an affector which computer modelling indicates will induce a conformation on the catalytic core of said first enzyme in which said invariant residues are closer to the coordinates of said template than the conformation induced by the affector designed in step (g), when said first enzyme is formed as a fourth complex with the affector designed in this step.

33. The method of Claim 32 wherein the affector of step (i) is the known affector of step (a).

34. The method of Claim 32, additionally comprising modifying the computer modelling used in step (g) in light of the data of step (j), prior to performing step (k).

35. The method of Claim 30, additionally comprising obtaining amino acid sequence data relating to the catalytic cores of the first and second enzymes.

36. The method of Claim 30 wherein step (f) comprises site directed mutagenesis of a recombinantly produced second enzyme.

37. The method of Claim 30, wherein the coordinates of said template are substantially as shown in Figure 17.

38. The method of Claim 30, wherein each of the affectors is an inhibitor.

39. The method of Claim 30, wherein said template includes coordinates separated by the distances substantially as shown in Table 4.

40. An affector prepared by the method of Claim 39.

41. A pharmaceutical composition comprising the affector of Claim 40.

42. A method of designing a specific inhibitor for a protein kinase, comprising:

obtaining data regarding the three-dimensional structure of a first protein kinase;

using said data in the design of an inhibitor for a second, different, protein kinase; and

producing said inhibitor.

43. The method of Claim 42 wherein said first protein kinase is cAMP dependent protein kinase or an analogue thereof.

44. The method of Claim 43, wherein the obtaining step comprises crystallizing a complex of cAMP dependent protein kinase and an inhibitor thereof.

45. The method of Claim 44, wherein the obtaining step additionally comprises obtaining X-ray crystallography data on the crystallized complex obtained from the crystallizing step.

46. The method of Claim 44, additionally comprising obtaining information regarding the structure of the crystallized complex obtained in the crystallizing step through circular dichroism, small angle neutron scattering, or other chemical procedures.

47. Use of the data of Figure 17 or of Table 4 in the design of an affector for a protein kinase.

48. A method of preparing a highly specific inhibitor of a first enzyme, said first enzyme being a member of a class of enzymes having a conserved catalytic core with a plurality of invariant residues, comprising:

a. identifying a second enzyme that is a member of said class and having a known first inhibitor thereof;

b. forming a first complex of said second enzyme and said first inhibitor;

c. obtaining data regarding the three dimensional coordinates of said invariant residues in said first complex;

d. designing a second inhibitor which computer modelling indicates will induce a conformation on the catalytic core of said first enzyme in which said invariant residues are in substantially the same coordinates as the coordinates obtained in step (c), when said first enzyme is formed as a second complex with said second inhibitor;

e. preparing said second inhibitor;

f. forming a third complex of said second inhibitor and a third enzyme complexable therewith, said third enzyme having a plurality of said invariant residues;

g. obtaining data regarding the three dimensional coordinates of said invariant residues in said third complex;

h. using the data obtained from step (g) to design a third inhibitor which computer modelling indicates will induce a conformation on the catalytic core of said first enzyme closer to that in which said invariant residues are in substantially the same coordinates as the coordinates obtained in step (c) than induced by the second inhibitor, when said first enzyme is formed as a fourth complex with said third inhibitor; and

i. producing said third inhibitor.

49. The method of Claim 48, wherein said first inhibitor is an inhibitory domain of said second enzyme.

50. The method of Claim 48, wherein said third enzyme comprises at least 5 invariant residues.

51. The method of Claim 48, wherein said third enzyme is a naturally occurring enzyme.

52. The method of Claim 48, wherein said third enzyme is a mutant enzyme.

53. A method of determining the efficacy of a first affector in affecting a first enzyme that is a member of a class of enzymes having a plurality of invariant residues among the members of said class, comprising:

determining the three dimensional coordinates of the invariant residues of a second enzyme in a first conformation wherein said second enzyme is in a complex with a second affector that is a strong affector of said enzyme;

determining the three dimensional coordinates of the invariant residues of said second enzyme in a second conformation wherein said enzyme is in a conformation other than said first conformation;

identifying the mobile invariant residues of said enzyme, said mobile invariant residues being those invariant residues at coordinates substantially different in said first conformation than in said second conformation;

determining the three dimensional coordinates of the mobile invariant residues of said first enzyme when said first enzyme is in a conformation wherein said first enzyme is in a complex with said first affector;

comparing the three dimensional coordinates of the mobile invariant residues of said first enzyme in said conformation with the coordinates of the mobile invariant residues of said enzyme in said first conformation, wherein relatively small differences in the coordinates indicate relatively high efficacy of said first affector.

54. The method of Claim 53, wherein the step of determining the coordinates of said first enzyme in said conformation is performed using computer modelling of said conformation.

55. The method of Claim 53, wherein the steps of determining the first and second conformations comprise obtaining X-ray crystallographic data of said enzyme.

56. The method of Claim 53, wherein said second conformation is a conformation produced by a ternary complex.

57. The method of Claim 56, wherein said ternary complex comprises a protein kinase, a nucleotide and an affector.

58. The method of Claim 53, wherein said second conformation is a conformation produced by said second enzyme not complexed with a ligand.

59. The method of Claim 53, wherein said second enzyme is the same enzyme as said first enzyme.

60. A method of designing specific inhibitors of a first protein kinase having a template defined by a plurality of invariant residues present in substantially all protein kinases, comprising:

obtaining data regarding the three dimensional coordinates of the invariant residues of a second protein kinase and of the points of contact between said second protein kinase and a known inhibitor thereof, said coordinates being obtained when said second protein kinase is formed as a complex with said known inhibitor;

generating a model of said first protein complex wherein said template is defined by the positions of said invariant residues in said complex;

examining the amino acid residues present in said first protein kinase at positions corresponding to the points of contact in said complex;

designing an inhibitor of said first protein kinase capable of forming ionic and hydrophobic interactions with said amino acid residues; and

producing said inhibitor of said first protein kinase.

61. The method of Claim 60, wherein said second protein kinase is cAMP dependent protein kinase.

62. The method of Claim 61, wherein said known inhibitor is PKI(5-24).

63. The method of Claim 62, wherein the points of contact in said complex comprise positions corresponding to the positions selected from the group consisting of P+1, P-2, P-3, P-6 and P-11 along said known inhibitor.

64. The method of Claim 60, wherein the positions corresponding to the points of contact in the examining step comprise positions within a sphere having a radius of 11 Å from the coordinates of the point of contact obtained in the obtaining step.

65. The method of Claim 64, wherein the positions corresponding to the points of contact in the examining step comprise positions within a sphere having a radius of 6 Å from the coordinates of the point of contact obtained in the obtaining step.

66. The method of Claim 60, wherein the designing step additionally comprises designing said inhibitor to form appropriate hydrogen bonding with said amino acid residues.

FIGURE 1

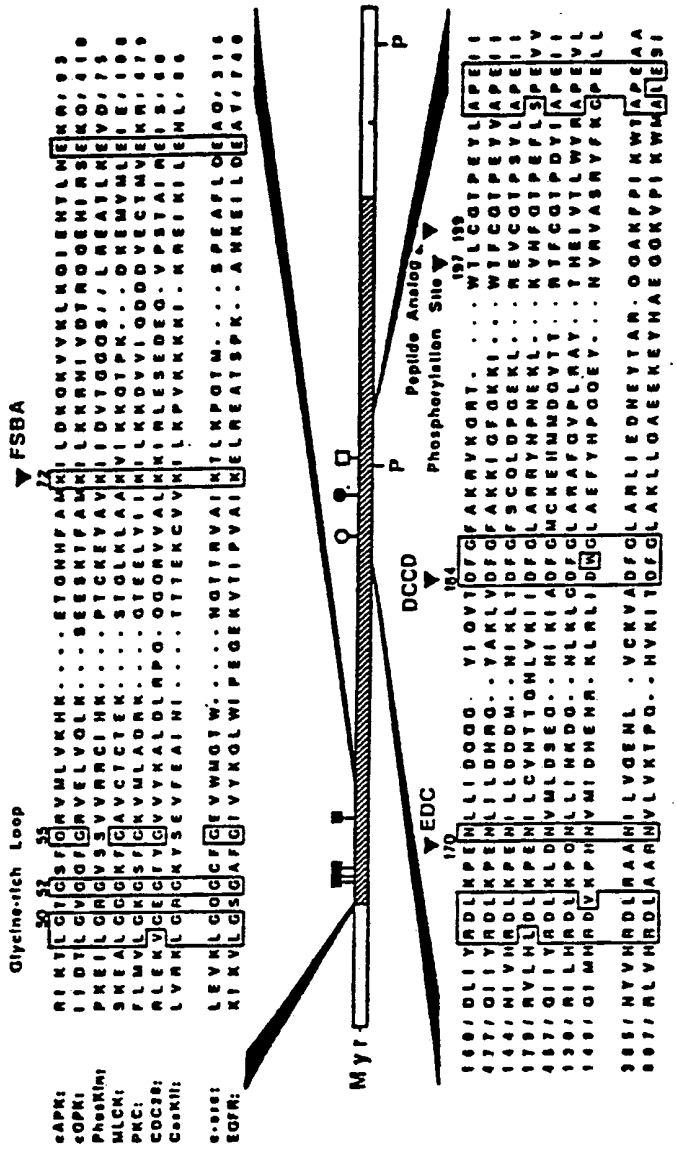
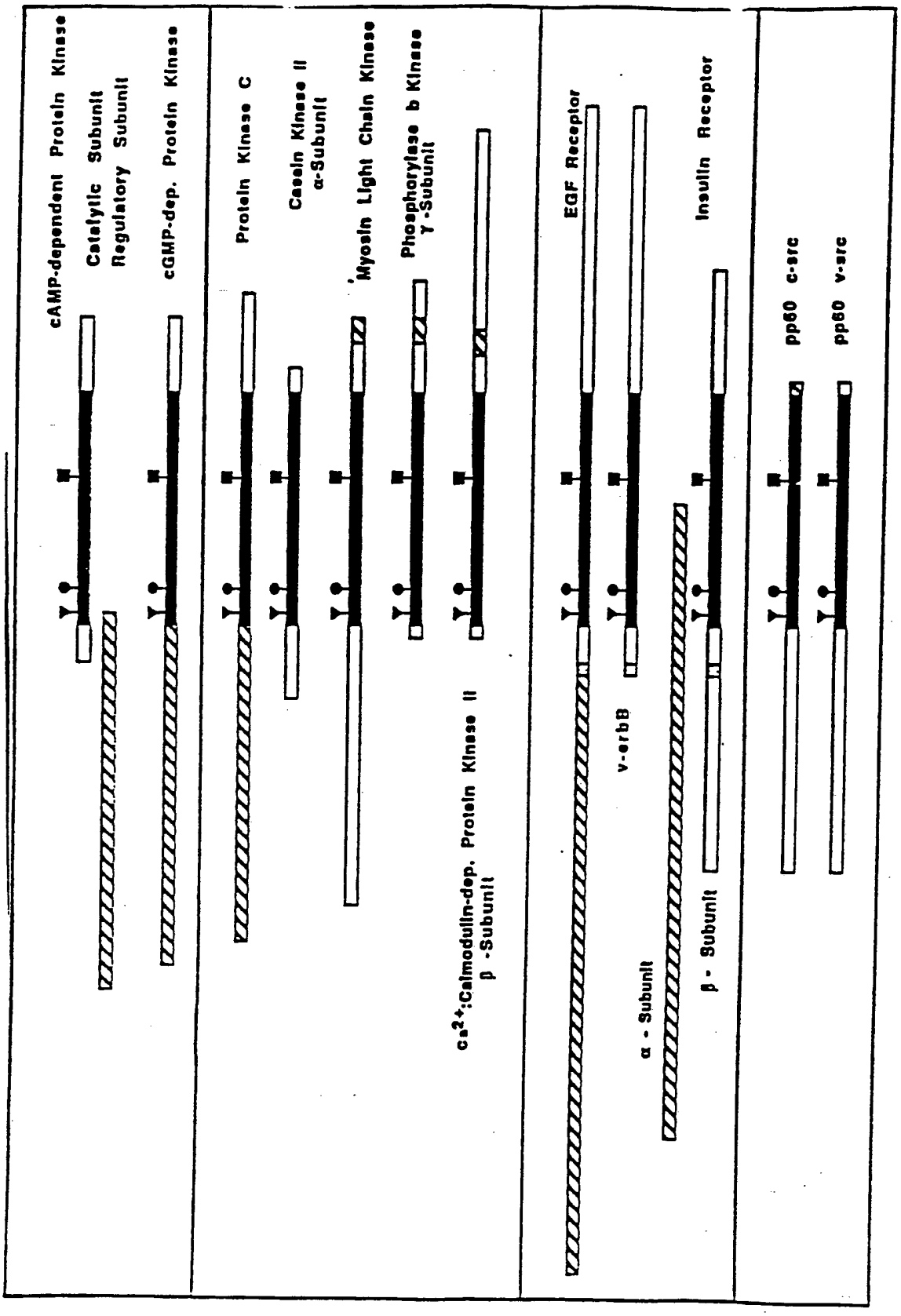

FSBA
Glycine-rich Loop
DCCD
EDC
Peptide Analog
Phosphorylation Site
Myr
P
P

FIGURE 2


cAMP-dependent Protein Kinase
Catalytic Subunit
Regulatory Subunit
cGMP-dep. Protein Kinase
Protein Kinase C
Casein Kinase II
α-Subunit
Myosin Light Chain Kinase
Phosphorylase b Kinase
γ-Subunit
Ca2+:Calmodulin-dep. Protein Kinase II
β-Subunit
EGF Receptor
v-erbB
α - Subunit
β - Subunit
Insulin Receptor
pp60 c-src
pp60 v-src

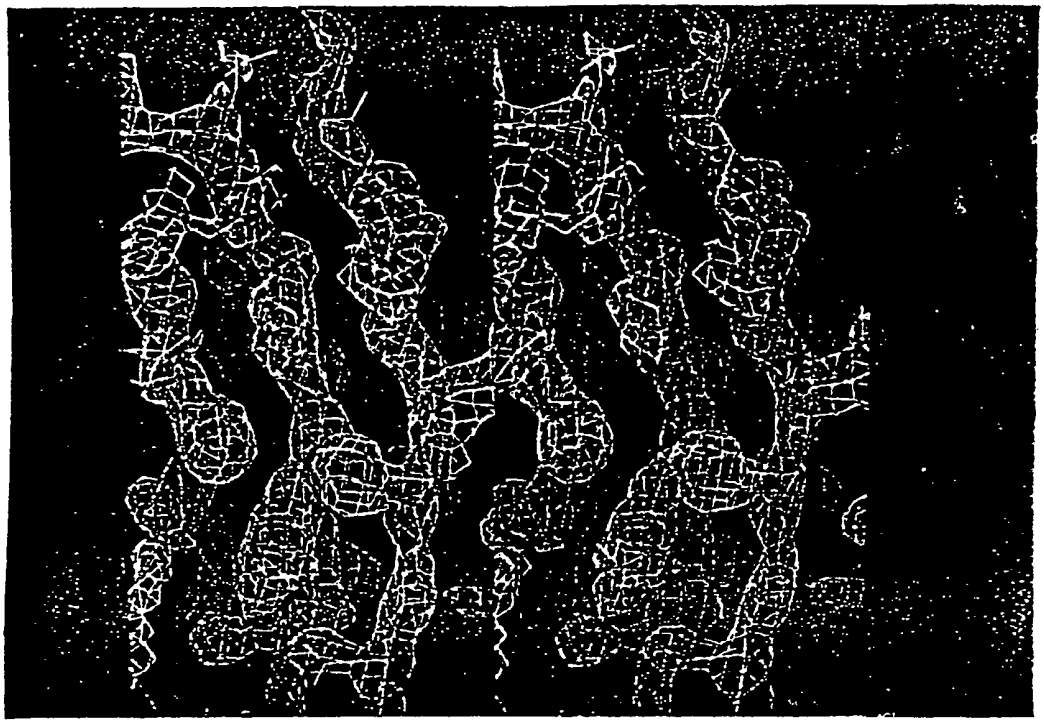


FIGURE 3A

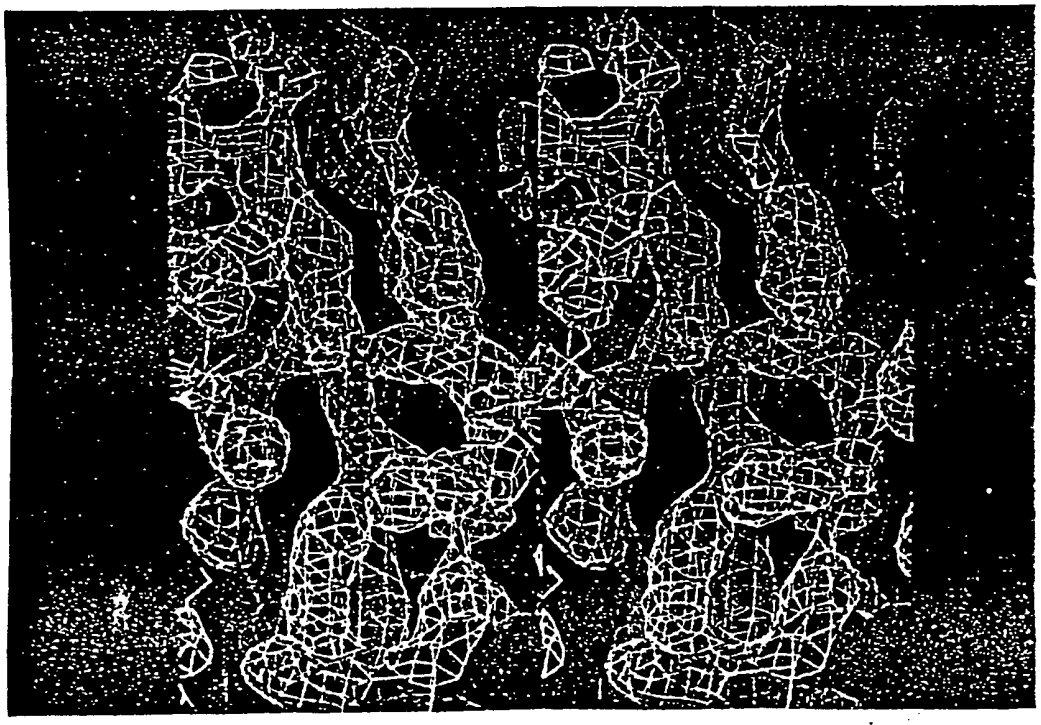
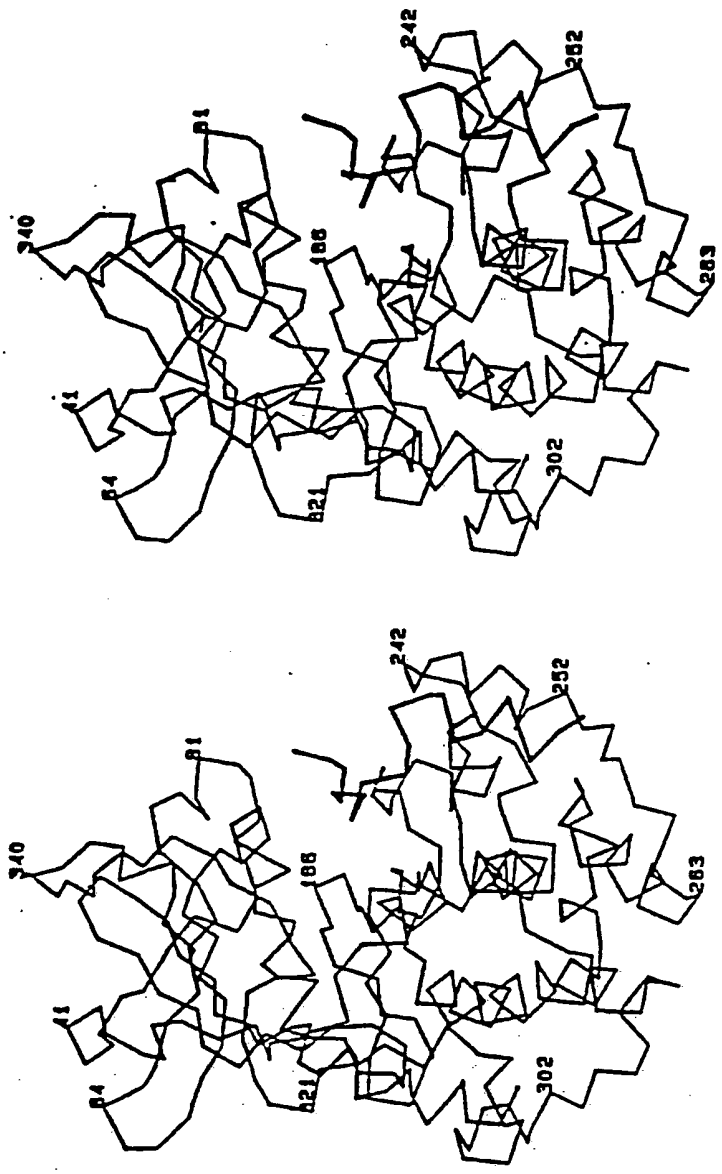


FIGURE 3B

FIGURE 4


242
252
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340
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263
41
84
302
321
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252
81
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84
302
321

FIGURE 5A

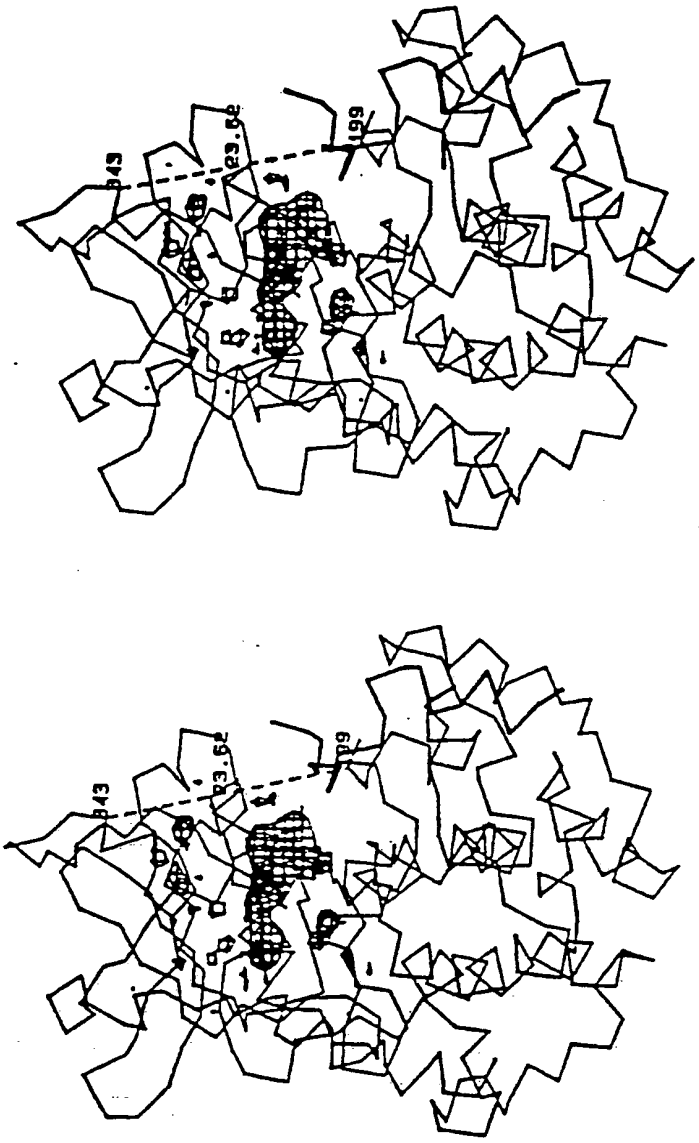
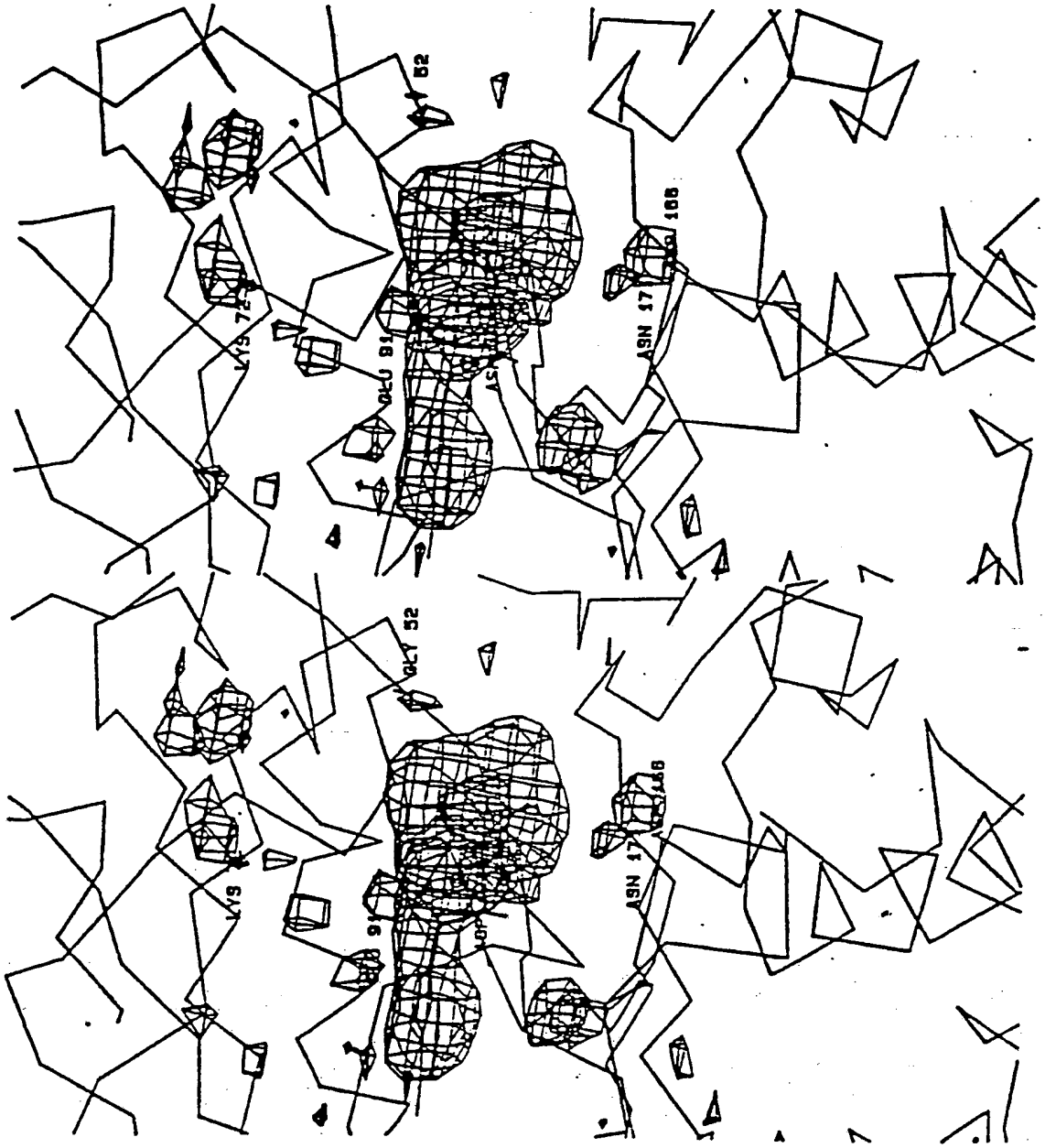


FIGURE 5B



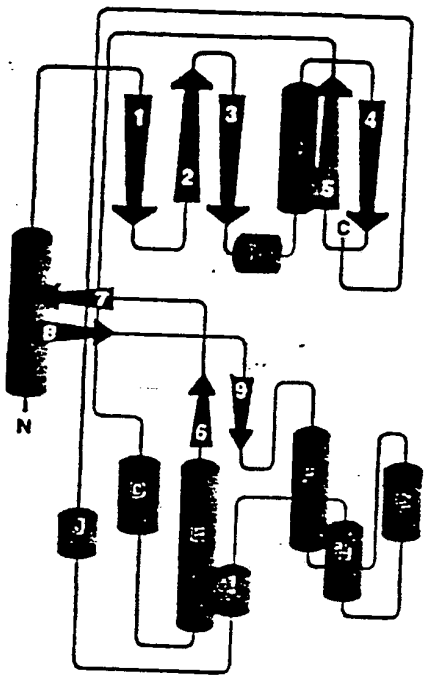


FIGURE 6

FIGURE 7B

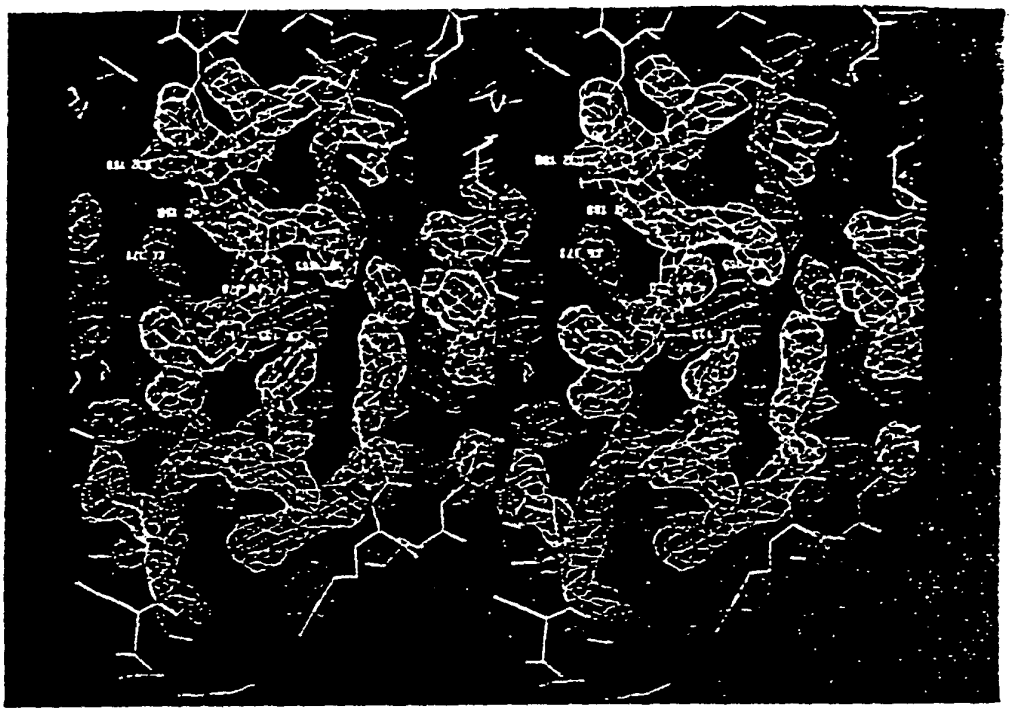
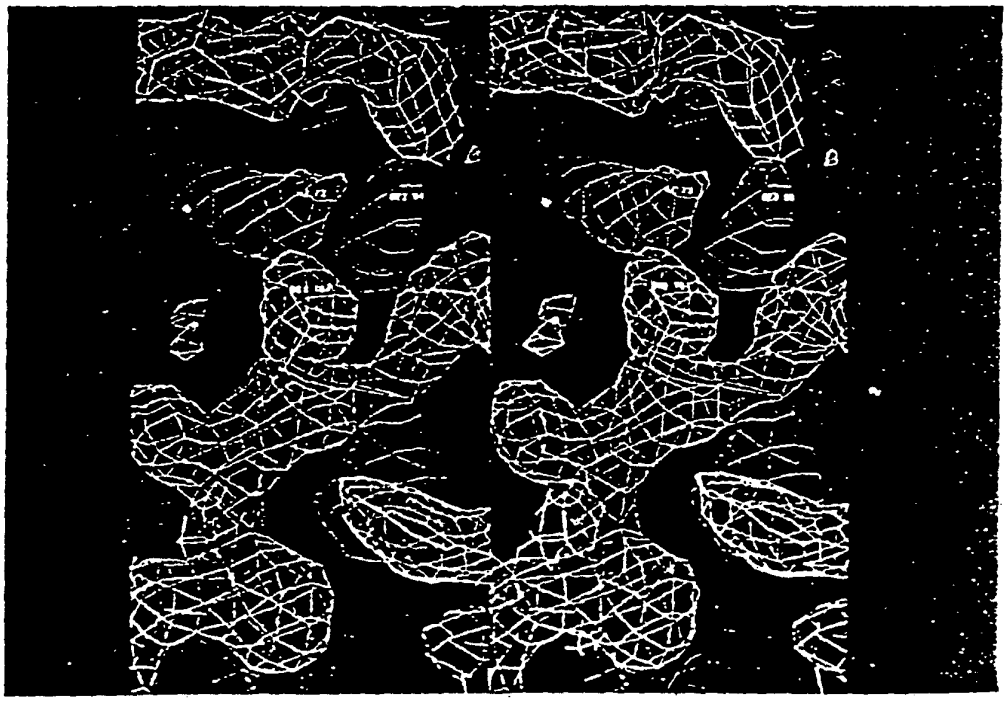


FIGURE 7A



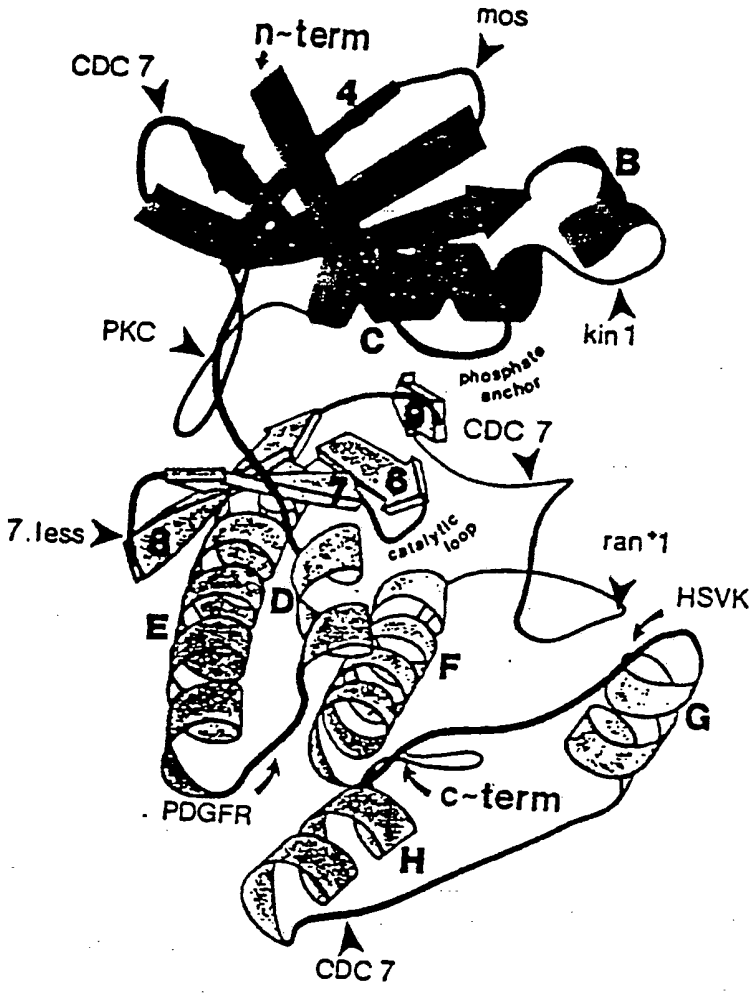

n~term
mos
CDC 7
4
B
PKC
C
kin 1
phosphate anchor
CDC 7
7
6
7.less
8
catalytic loop
ran*1
HSVK
D
E
F
G
PDGFR
c~term
H
CDC 7

FIGURE 8B

FIGURE 8A

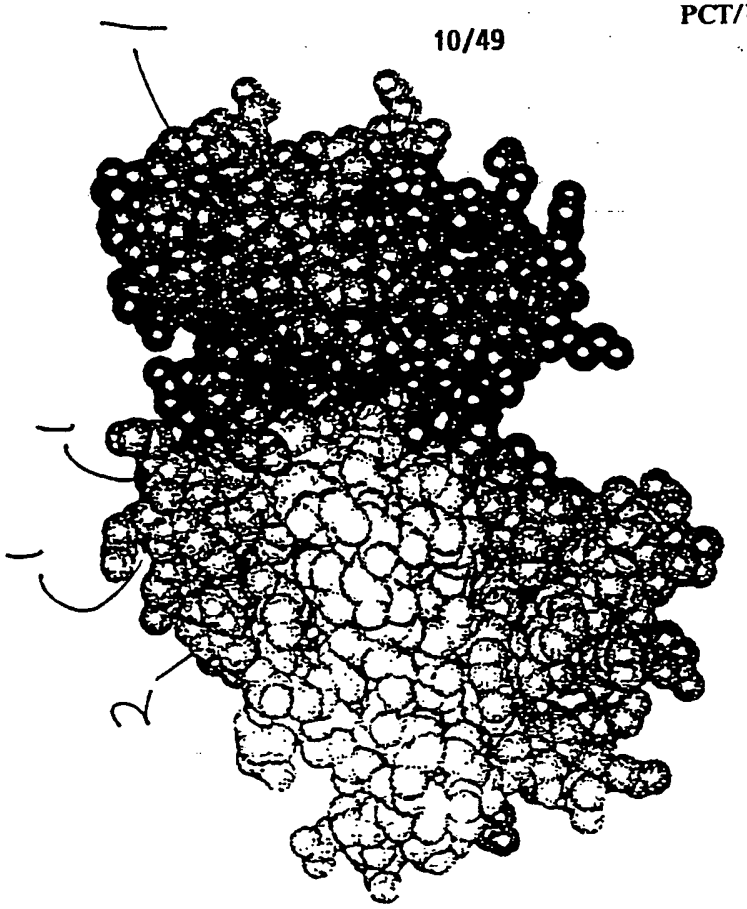
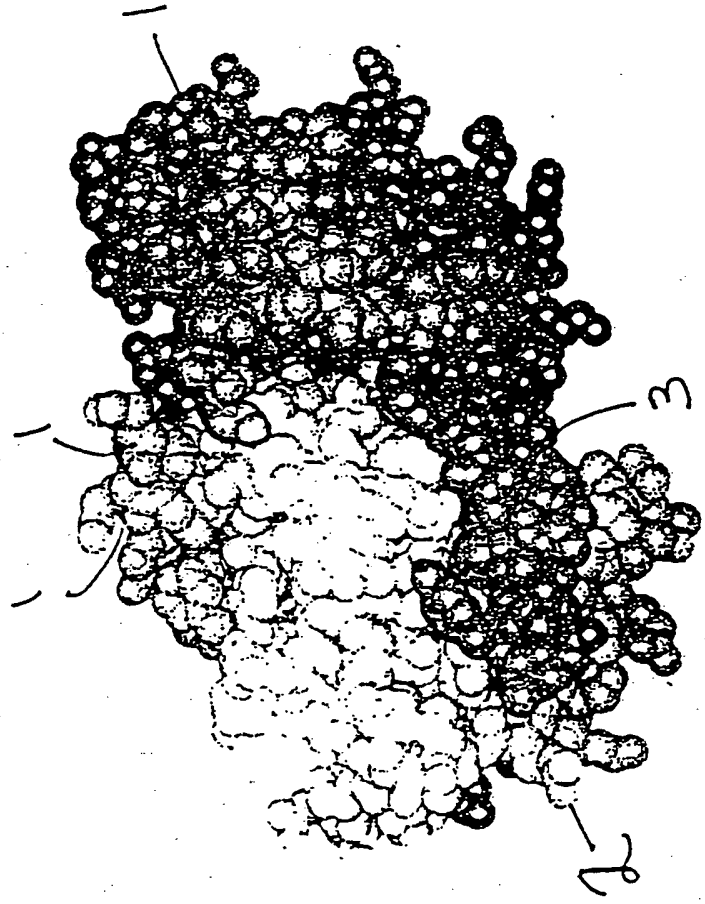


FIGURE 8C



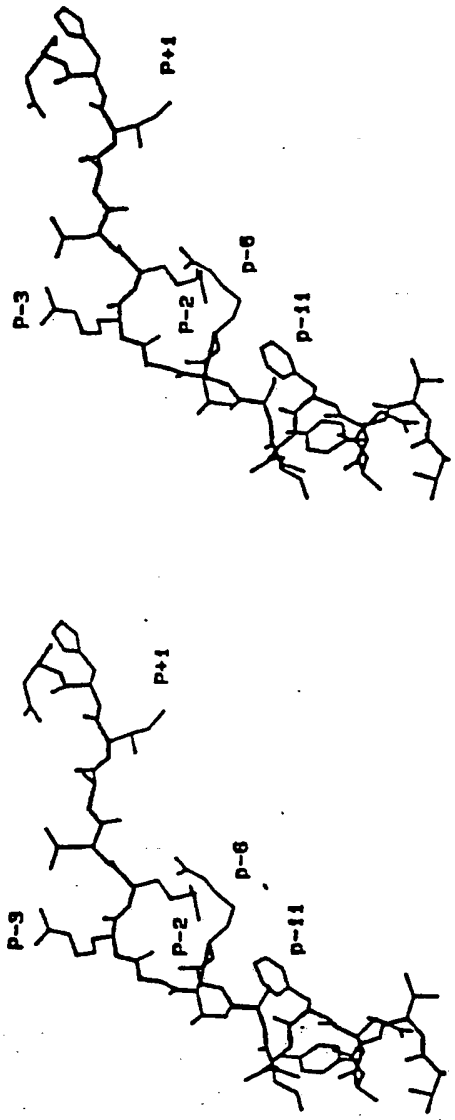


FIGURE 9

FIGURE 10A

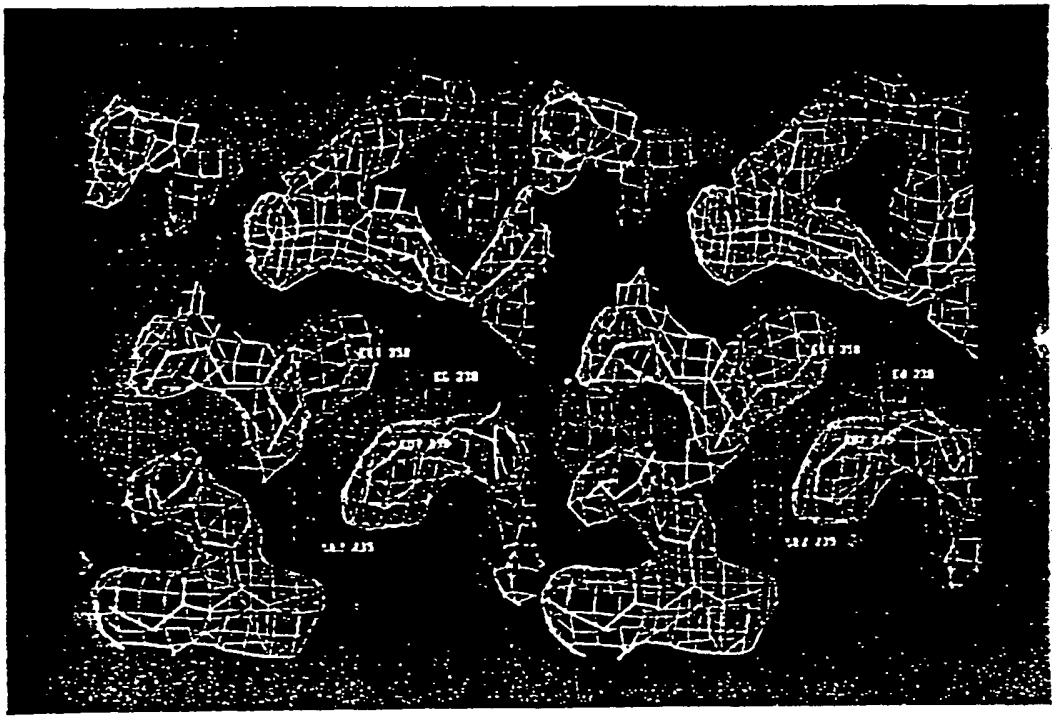
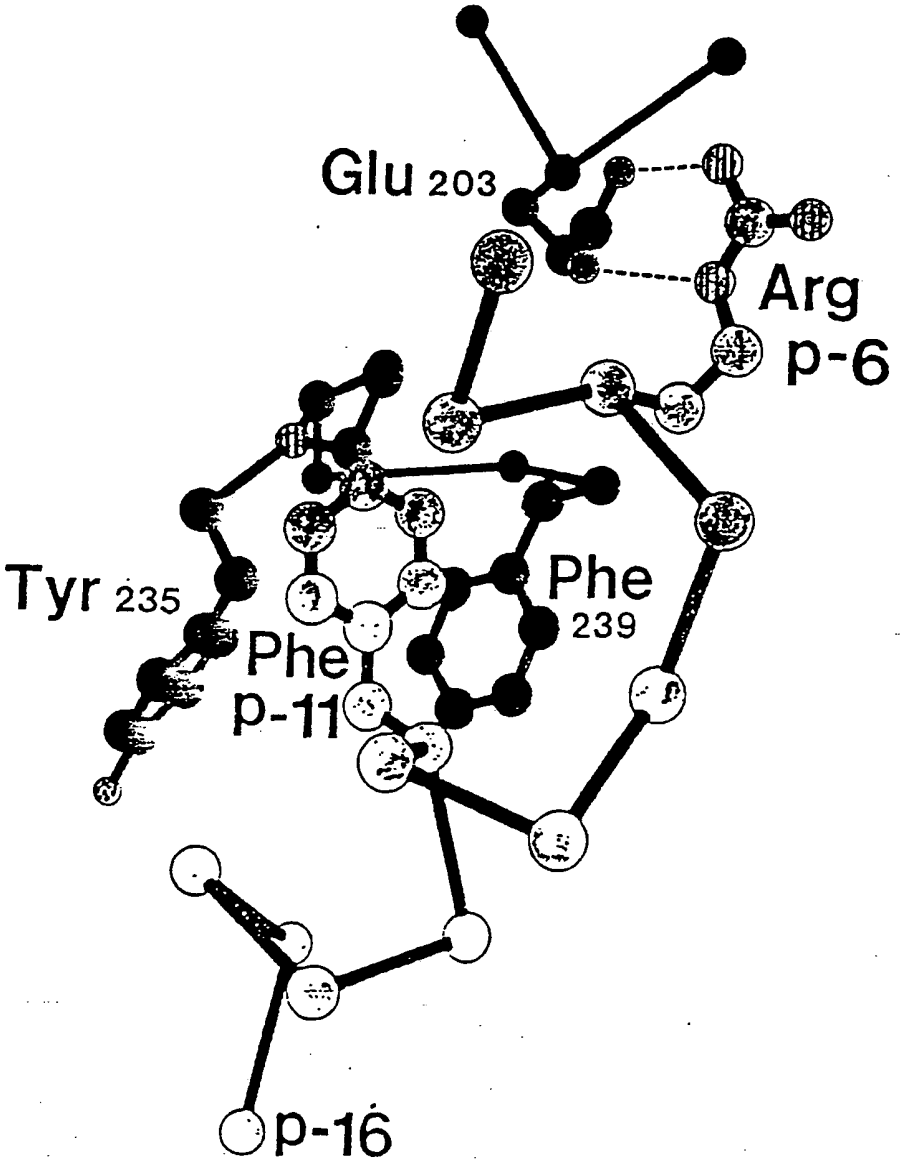


FIGURE 10B



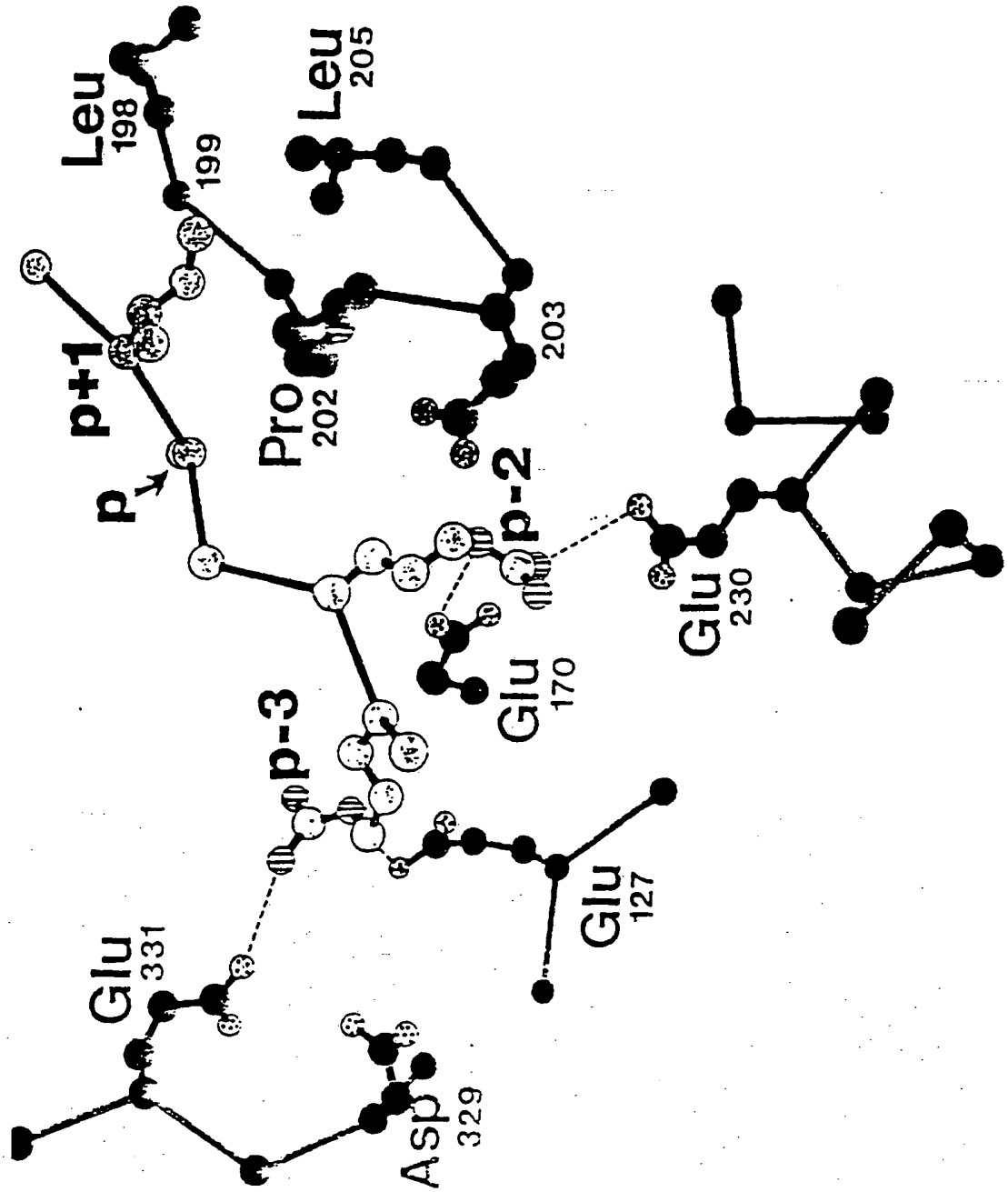

Leu
198
199
Leu
205
p+1
p
Pro
202
203
p-2
Glu
230
Glu
170
p-3
Glu
127
Glu
331
Asp
329

FIGURE 11

FIGURE 12B

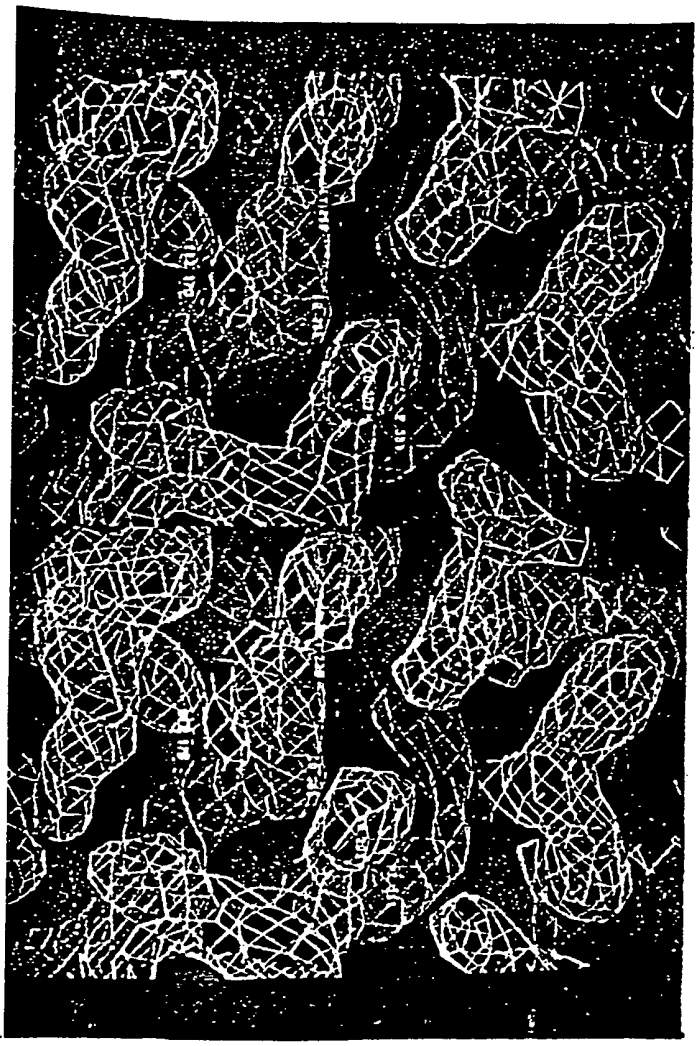


FIGURE 12A

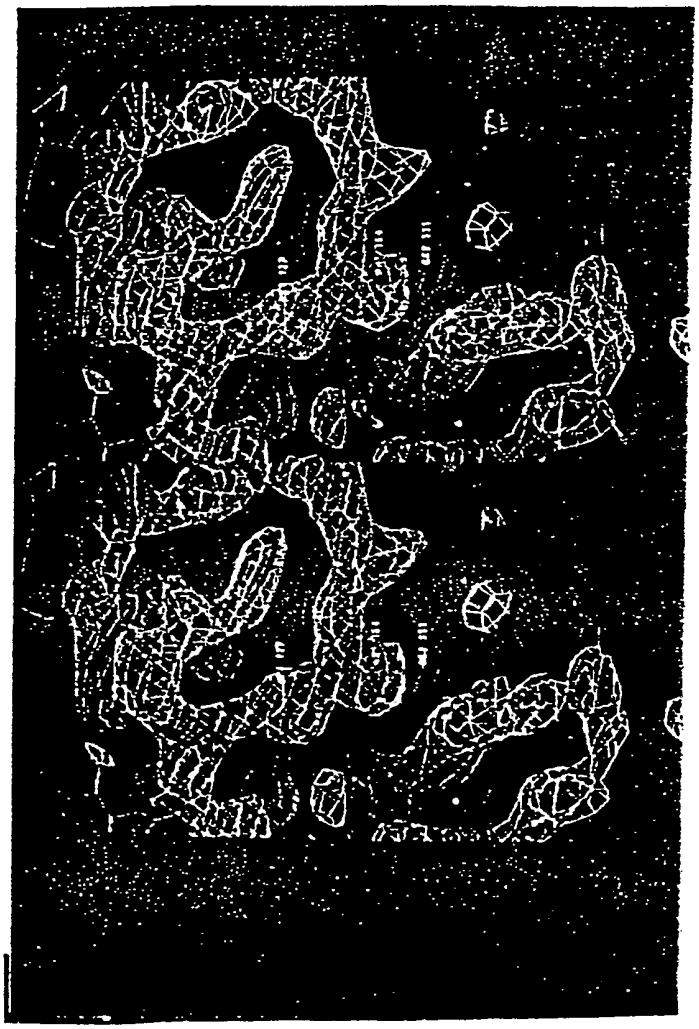


FIGURE 12C

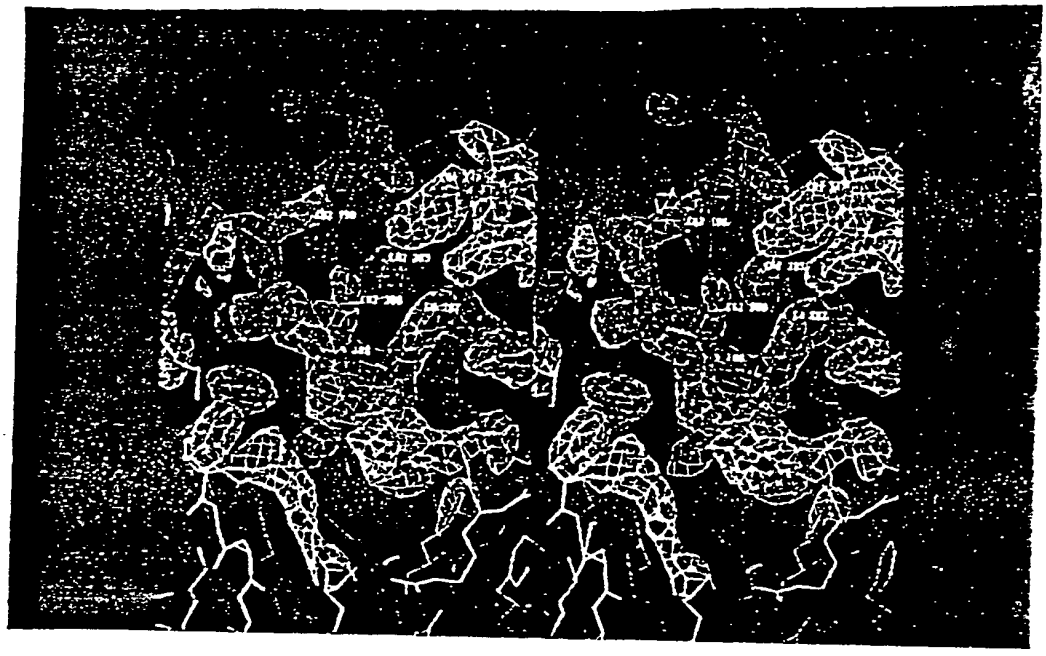


FIGURE 13A

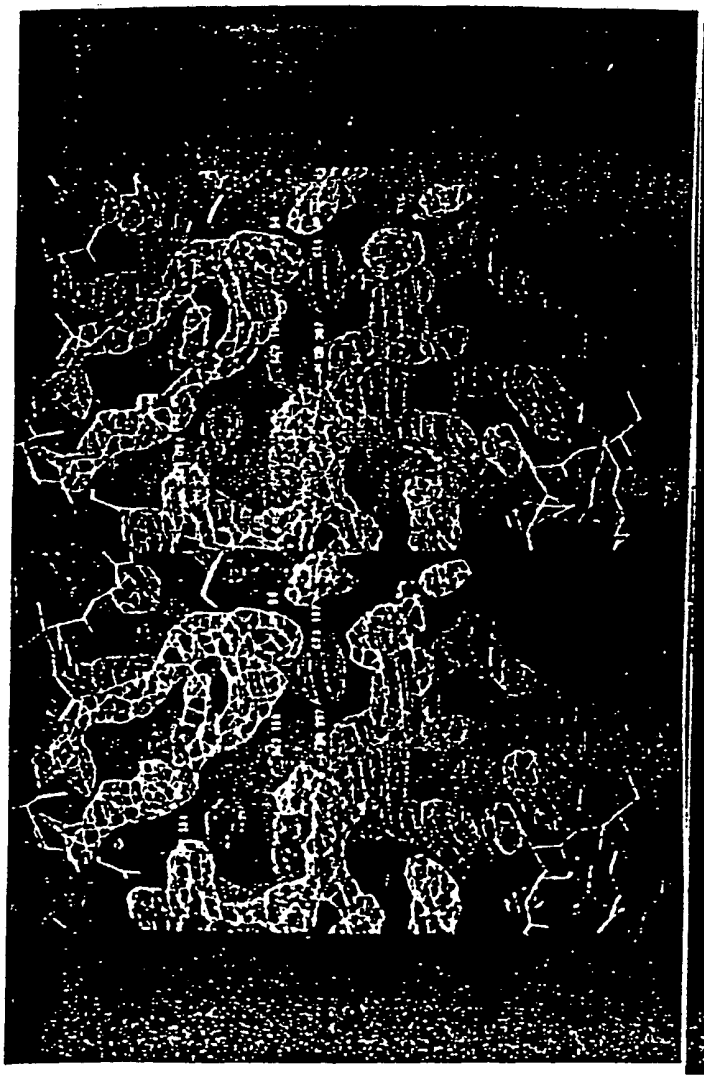
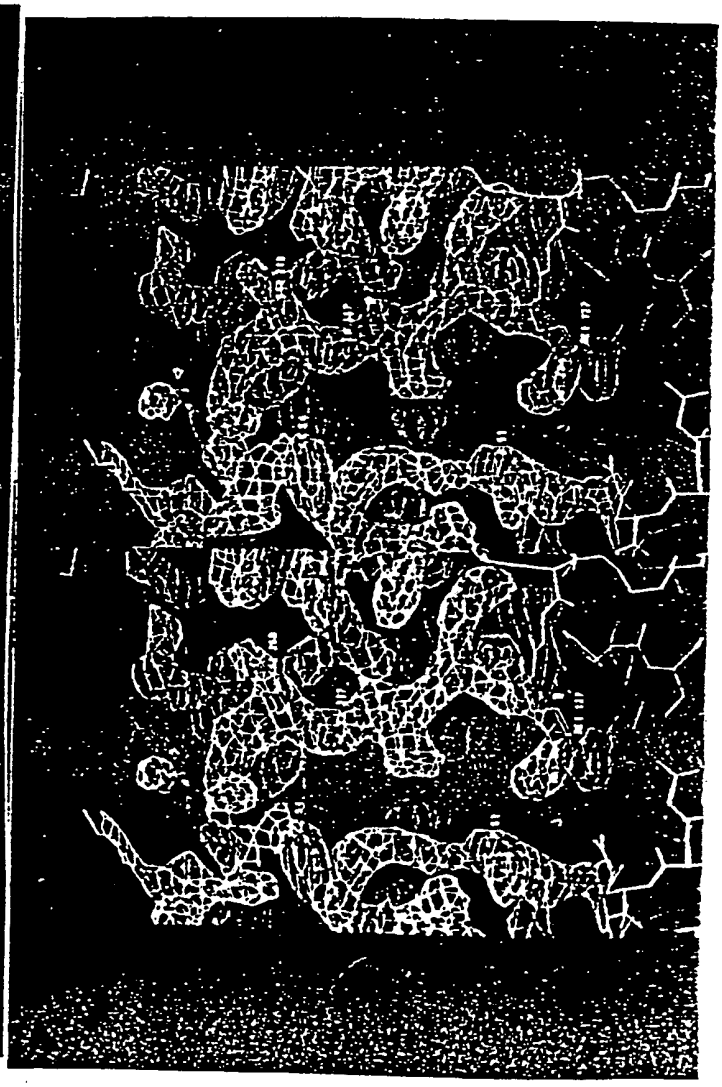


FIGURE 13B



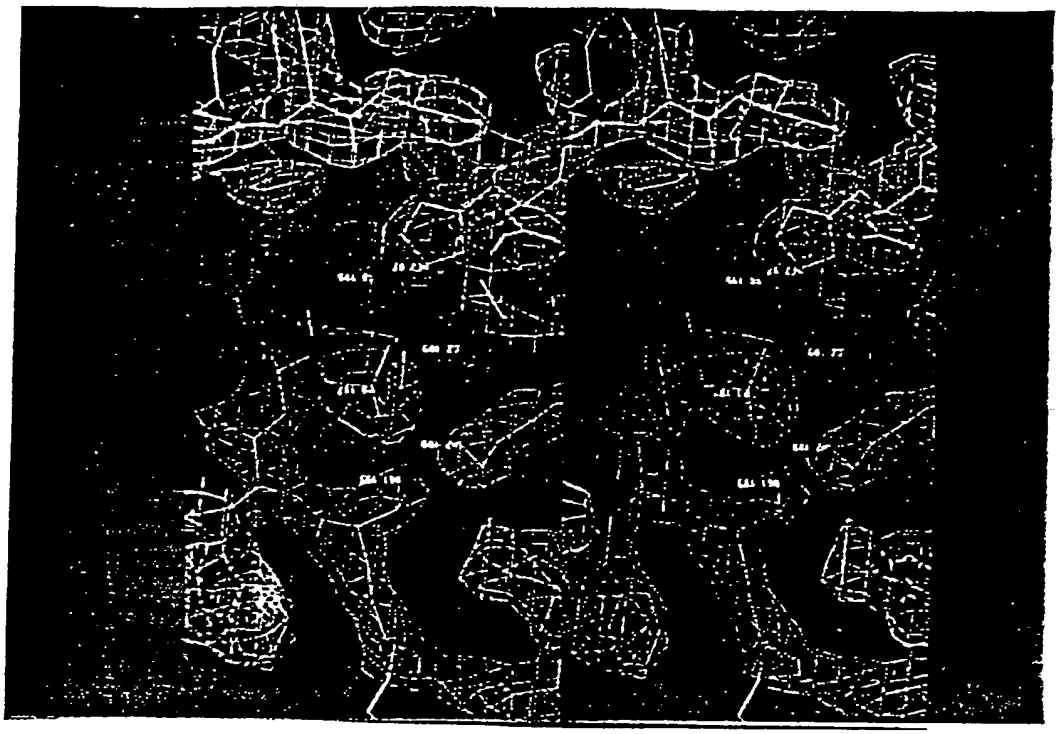
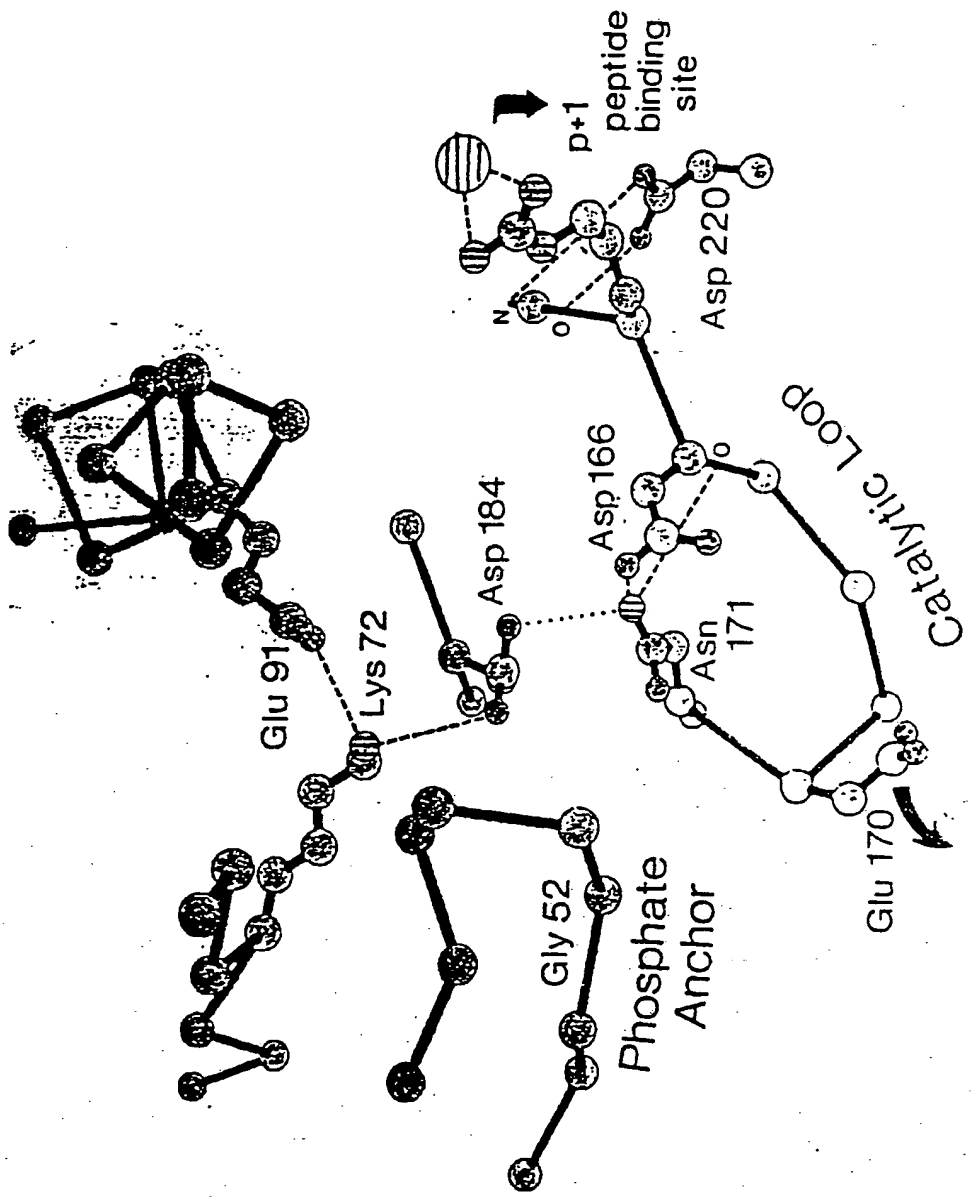


FIGURE 13C


p+1
peptide
binding
site
Asp 220
Asp 166
Asp 184
Glu 91
Lys 72
Asn
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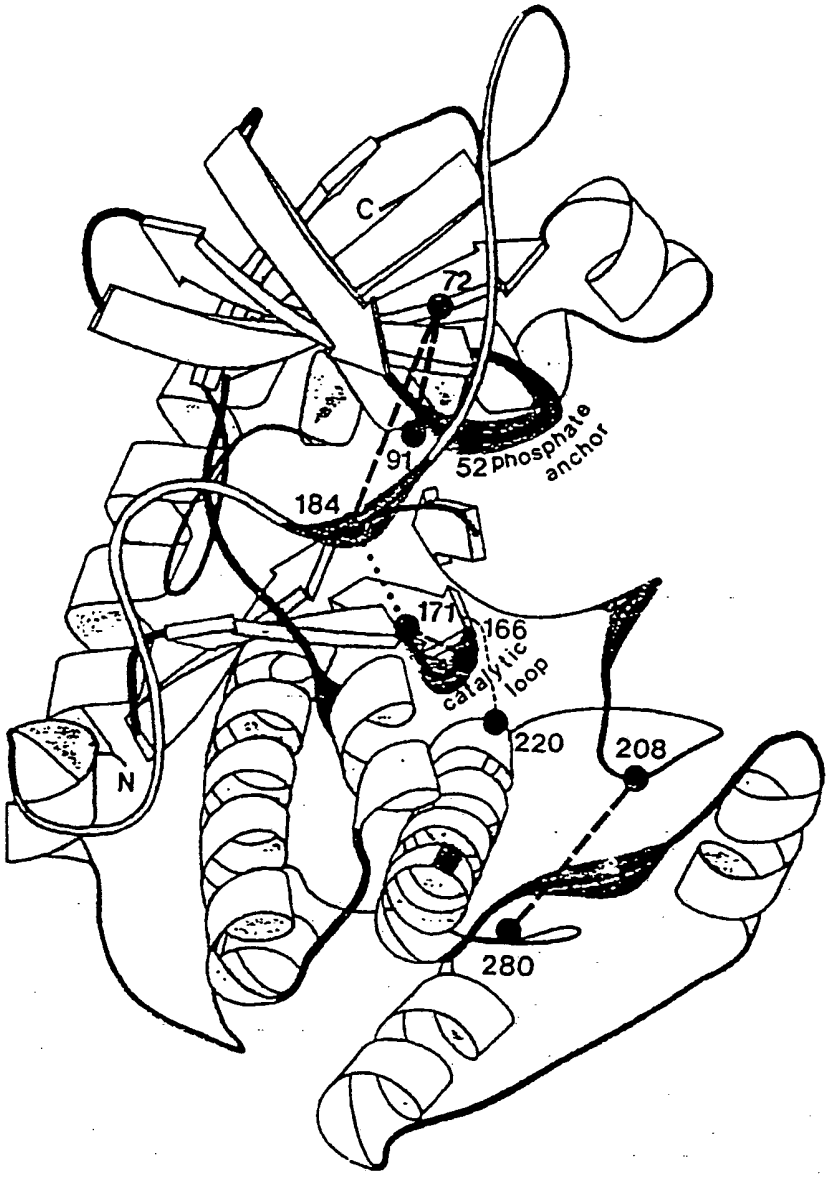
Catalytic Loop
Gly 52
Phosphate
Anchor
Glu 170
p-2
peptide binding site

FIGURE 14


C
72
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phosphate anchor
184
171
166
catalytic loop
220
208
N
280

FIGURE 15

FIGURE 16

PKI(5-24)

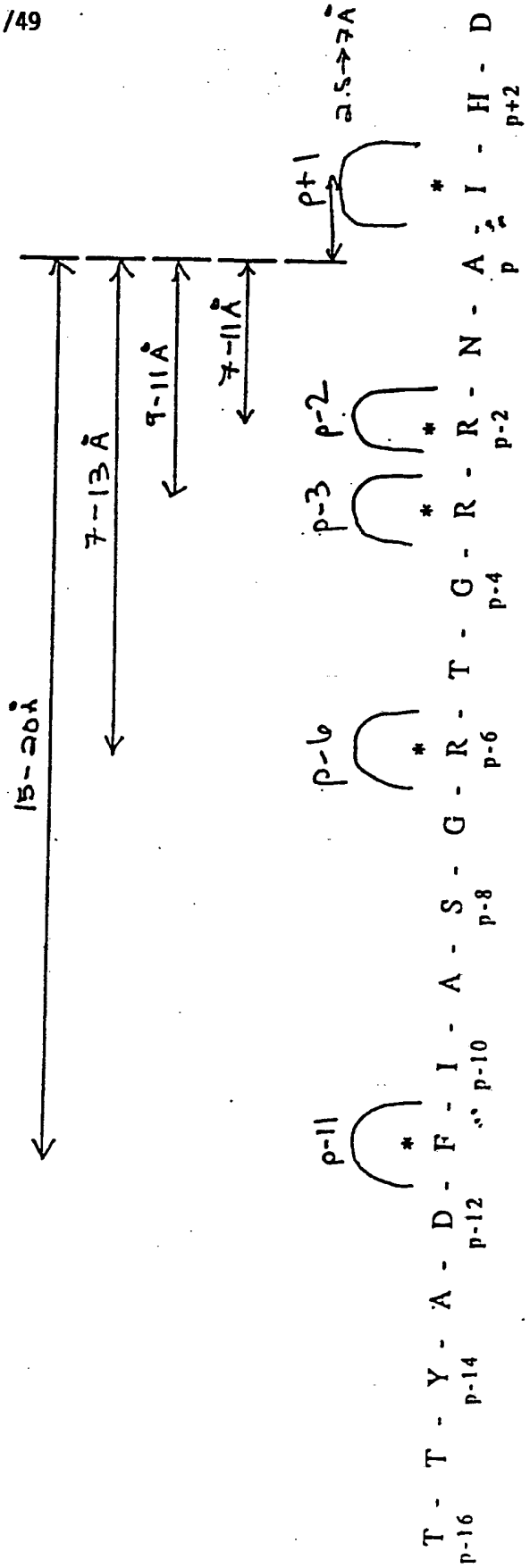

FIGURE 17

Coordinates of Catalytic Subunit of cAMP-dependent Protein Kinase (Residues 15-350) Complexed with PKI(5-24) (Residues 331-370)

ATOM	1	N	VAL	15	-5.253	-10.934	-12.585	1.00 17.60
ATOM	2	CA	VAL	15	-3.967	-10.783	-13.261	1.00 17.60
ATOM	3	CB	VAL	15	-3.226	-12.141	-13.183	1.00 17.60
ATOM	4	CG1	VAL	15	-1.737	-11.768	-13.430	1.00 17.60
ATOM	5	CG2	VAL	15	-3.523	-12.950	-11.871	1.00 17.60
ATOM	6	C	VAL	15	-4.211	-10.316	-14.716	1.00 17.60
ATOM	7	O	VAL	15	-4.787	-9.210	-14.806	1.00 17.60
ATOM	8	N	LYS	16	-3.916	-11.140	-15.767	1.00 17.60
ATOM	9	CA	LYS	16	-4.109	-10.950	-17.248	1.00 17.60
ATOM	10	CB	LYS	16	-4.590	-12.285	-17.900	1.00 17.60
ATOM	11	CG	LYS	16	-3.765	-13.627	-17.732	1.00 17.60
ATOM	12	CD	LYS	16	-4.563	-14.710	-18.529	1.00 17.60
ATOM	13	CE	LYS	16	-4.104	-16.178	-18.413	1.00 17.60
ATOM	14	NZ	LYS	16	-5.113	-17.148	-18.865	1.00 17.60
ATOM	15	C	LYS	16	-5.101	-9.845	-17.609	1.00 17.60
ATOM	16	O	LYS	16	-4.845	-8.749	-18.115	1.00 17.60
TOM	17	N	GLU	17	-6.223	-10.208	-17.038	1.00 17.60
.OM	18	CA	GLU	17	-7.386	-9.372	-16.920	1.00 17.60
..TOM	19	CB	GLU	17	-8.277	-10.047	-15.773	1.00 17.60
ATOM	20	CG	GLU	17	-7.484	-10.689	-14.607	1.00 17.60
ATOM	21	CD	GLU	17	-8.290	-11.406	-13.533	1.00 17.60
ATOM	22	OE1	GLU	17	-8.492	-12.620	-13.634	1.00 17.60
ATOM	23	OE2	GLU	17	-8.704	-10.739	-12.578	1.00 17.60
ATOM	24	C	GLU	17	-7.174	-7.872	-16.681	1.00 17.60
ATOM	25		GLU	17	-7.072	-7.008	-17.561	1.00 17.60
ATOM	26	N	PHE	18	-7.012	-7.590	-15.395	1.00 17.60
ATOM	27	CA	PHE	18	-7.303	-6.244	-14.915	1.00 17.60
ATOM	28	CB	PHE	18	-7.548	-6.403	-13.459	1.00 17.60
ATOM	29	CG	PHE	18	-7.123	-5.200	-12.709	1.00 17.60
ATOM	30	CD1	PHE	18	-7.725	-3.995	-12.998	1.00 17.60
ATOM	31	CD2	PHE	18	-6.875	-5.360	-11.808	1.00 17.60
ATOM	32	CE1	PHE	18	-7.241	-2.867	-12.356	1.00 17.60
ATOM	33	CE2	PHE	18	-5.593	-4.220	-11.164	1.00 17.60
ATOM	34	CZ	PHE	18	-6.180	-2.982	-11.442	1.00 17.60
ATOM	35	C	PHE	18	-5.758	-5.614	-15.166	1.00 17.60
ATOM	36	O	PHE	18	-5.688	-4.424	-15.497	1.00 17.60
ATOM	37	N	LEU	19	-4.702	-6.401	-15.176	1.00 17.60
ATOM	38	CA	LEU	19	-3.423	-5.823	-15.495	1.00 17.60
ATOM	39	CB	LEU	19	-2.384	-6.911	-15.303	1.00 17.60
ATOM	40	CG	LEU	19	-1.190	-6.499	-14.424	1.00 17.60
ATOM	41	CD1	LEU	19	-1.617	-6.126	-13.015	1.00 17.60
TOM	42	CD2	LEU	19	-0.232	-7.661	-14.368	1.00 17.60
OM	43	C	LEU	19	-3.392	-5.214	-16.930	1.00 17.60
..OM	44	O	LEU	19	-2.456	-4.478	-17.344	1.00 17.60
ATOM	45	N	ALA	20	-4.487	-5.517	-17.658	1.00 17.60
ATOM	46	CA	ALA	20	-4.700	-5.023	-18.988	1.00 17.60
ATOM	47	CB	ALA	20	-5.381	-6.062	-19.841	1.00 17.60
ATOM	48	C	ALA	20	-5.557	-3.808	-18.953	1.00 17.60
ATOM	49	O	ALA	20	-5.185	-2.825	-19.695	1.00 17.60
ATOM	50	N	LYS	21	-6.654	-3.785	-18.200	1.00 17.60
ATOM	51	CA	LYS	21	-7.429	-2.549	-18.149	1.00 17.60
ATOM	52	CB	LYS	21	-8.651	-2.726	-17.314	1.00 17.60
ATOM	53	CG	LYS	21	-9.460	-1.429	-17.387	1.00 17.60
ATOM	54	CD	LYS	21	-10.091	-1.202	-16.018	1.00 17.60
ATOM	55	CE	LYS	21	-10.740	0.173	-15.965	1.00 17.60
ATOM	56	NZ	LYS	21	-11.272	0.421	-14.591	1.00 17.60
ATOM	57	C	LYS	21	-6.589	-1.426	-17.552	1.00 17.60
ATOM	58	O	LYS	21	-6.708	-0.248	-17.920	1.00 17.60
ATOM	59	N	ALA	22	-5.693	-1.848	-16.645	1.00 17.60
ATOM	60	CA	ALA	22	-4.712	-0.950	-16.079	1.00 17.60
ATOM	61	CB	ALA	22	-3.981	-1.619	-15.000	1.00 17.60
ATOM	62	C	ALA	22	-3.692	-0.679	-17.132	1.00 17.60
ATOM	63	O	ALA	22	-3.283	0.697	-17.114	1.00 17.60
ATOM	64	N	LYS	23	-3.275	-1.311	-18.109	1.00 17.60
ATOM	65	CA	LYS	23	-2.296	-0.925	-19.116	1.00 17.60
ATOM	66	CB	LYS	23	-2.160	-2.006	-20.166	1.00 17.60
ATOM	67	CG	LYS	23	-0.876	-2.829	-20.085	1.00 17.60
ATOM	68	CD	LYS	23	0.264	-2.286	-21.013	1.00 17.60
ATOM	69	CE	LYS	23	1.564	-3.161	-20.830	1.00 17.60
ATOM	70	NZ	LYS	23	2.778	-2.680	-21.509	1.00 17.60
ATOM	71	C	LYS	23	-2.753	0.347	-19.782	1.00 17.60
ATOM	72	O	LYS	23	-2.080	1.395	-19.778	1.00 17.60
ATOM	73	N	GLU	24	-3.999	0.273	-20.260	1.00 17.60
ATOM	74	CA	GLU	24	-4.471	1.361	-21.054	1.00 17.60
ATOM	75	CB	GLU	24	-5.708	0.950	-21.860	1.00 17.60
ATOM	76	CG	GLU	24	-5.518	0.187	-23.234	1.00 17.60
ATOM	77	CD	GLU	24	-5.260	1.089	-24.554	1.00 17.60
ATOM	78	OE1	GLU	24	-6.038	0.872	-25.539	1.00 17.60
ATOM	79	OE2	GLU	24	-4.271	1.780	-24.609	1.00 17.60
ATOM	80	C	GLU	24	-4.763	2.572	-20.237	1.00 17.60
ATOM	81	O	GLU	24	-4.713	3.583	-20.917	1.00 17.60
ATOM	82	N	ASP	25	-5.054	2.715	-18.923	1.00 17.60
ATOM	83	CA	ASP	25	-5.172	4.111	-18.475	1.00 17.60
ATOM	84	CB	ASP	25	-6.061	4.402	-17.197	1.00 17.60
ATOM	85	CG	ASP	25	-6.755	5.833	-17.305	1.00 17.60
ATOM	86	OD1	ASP	25	-7.190	6.226	-18.412	1.00 17.60
ATOM	87	OD2	ASP	25	-6.869	6.599	-16.326	1.00 17.60
ATOM	88	C	ASP	25	-3.776	4.616	-18.172	1.00 17.60
ATOM	89	O	ASP	25	-3.517	5.816	-18.355	1.00 17.60
ATOM	90	N	PHE	26	-2.839	3.692	-17.828	1.00 17.60
ATOM	91	CA	PHE	26	-1.435	4.056	-17.600	1.00 17.60
ATOM	92	CB	PHE	26	-0.463	2.849	-17.432	1.00 17.60
ATOM	93	CG	PHE	26	0.935	3.360	-17.127	1.00 17.60
ATOM	94	CD1	PHE	26	1.212	3.892	-15.886	1.00 17.60
ATOM	95	CD2	PHE	26	1.900	3.393	-18.112	1.00 17.60
ATOM	96	CE1	PHE	26	2.435	4.461	-15.644	1.00 17.60
ATOM	97	CE2	PHE	26	3.122	3.965	-17.868	1.00 17.60
ATOM	98	CZ	PHE	26	3.379	4.498	-16.636	1.00 17.60
ATOM	99	C	PHE	26	-1.015	4.701	-18.865	1.00 17.60
ATOM	100	O	PHE	26	-0.778	5.889	-18.814	1.00 17.60
ATOM	101	N	LEU	27	-1.055	4.161	-20.045	1.00 17.60
ATOM	102	CA	LEU	27	-0.489	4.835	-21.202	1.00 17.60
ATOM	103	CB	LEU	27	-0.510	3.902	-22.403	1.00 17.60
ATOM	104	CG	LEU	27	0.637	2.887	-22.666	1.00 17.60
ATOM	105	CD1	LEU	27	1.089	2.149	-21.440	1.00 17.60
ATOM	106	CD2	LEU	27	0.105	1.787	-23.556	1.00 17.60
ATOM	107	C	LEU	27	-1.203	6.118	-21.510	1.00 17.60
ATOM	108	O	LEU	27	-0.552	7.026	-22.015	1.00 17.60
ATOM	109	N	LYS	28	-2.435	6.302	-21.032	1.00 17.60
ATOM	110	CA	LYS	28	-3.159	7.519	-21.341	1.00 17.60
ATOM	111	CB	LYS	28	-4.656	7.284	-21.168	1.00 17.60
ATOM	112	CG	LYS	28	-5.341	8.471	-21.861	1.00 17.60
ATOM	113	CD	LYS	28	-6.891	8.434	-21.941	1.00 17.60
ATOM	114	CE	LYS	28	-7.199	9.856	-22.878	1.00 17.60
ATOM	115	NZ	LYS	28	-8.624	10.124	-23.078	1.00 17.60
ATOM	116	C	LYS	28	-2.715	8.668	-20.475	1.00 17.60
ATOM	117	O	LYS	28	-2.633	9.803	-20.916	1.00 17.60
ATOM	118	N	LYS	29	-2.399	8.379	-19.240	1.00 17.60
ATOM	119	CA	LYS	29	-1.937	9.392	-18.347	1.00 17.60
ATOM	120	CB	LYS	29	-2.160	8.957	-16.932	1.00 17.60
ATOM	121	CG	LYS	29	-3.635	8.800	-16.716	1.00 17.60
ATOM	122	CD	LYS	29	-4.055	8.441	-15.327	1.00 17.60
ATOM	123	CE	LYS	29	-4.616	9.689	-14.674	1.00 17.60
ATOM	124	NZ	LYS	29	-5.363	9.369	-13.445	1.00 17.60
ATOM	125	C	LYS	29	-0.659	9.582	-18.608	1.00 17.60
ATOM	126	O	LYS	29	0.117	10.669	-18.509	1.00 17.60
ATOM	127	N	TRP	30	0.184	8.498	-19.036	1.00 17.60

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ATOM  128  CA  TRP  30       1.608   8.431 -19.342  1.00 17.60
ATOM  129  CB  TRP  30       1.945   7.029 -19.784  1.00 17.60
ATOM  130  CG  TRP  30       3.397   6.884 -20.180  1.00 17.60
ATOM  131  CD2 TRP  30       4.475   6.972 -19.343  1.00 17.60
ATOM  132  CE2 TRP  30       5.509   6.989 -20.257  1.00 17.60
ATOM  133  CE3 TRP  30       4.737   7.062 -18.000  1.00 17.60
ATOM  134  CD1 TRP  30       3.726   6.803 -21.497  1.00 17.60
ATOM  135  NE1 TRP  30       5.025   6.885 -21.497  1.00 17.60
ATOM  136  CZ2 TRP  30       6.828   7.111 -19.865  1.00 17.60
ATOM  137  CZ3 TRP  30       6.056   7.182 -17.587  1.00 17.60
ATOM  138  CH2 TRP  30       7.089   7.212 -18.501  1.00 17.60
ATOM  139  C   TRP  30       1.993   9.388 -20.420  1.00 17.60
ATOM  140  O   TRP  30       3.107   9.868 -20.501  1.00 17.60
ATOM  141  N   GLU  31       1.056   9.587 -21.311  1.00 17.60
ATOM  142  CA  GLU  31       1.262  10.417 -22.451  1.00 17.60
ATOM  143  CB  GLU  31       0.404   9.918 -23.608  1.00 17.60
ATOM  144  CG  GLU  31       1.180   8.804 -24.289  1.00 17.60
ATOM  145  CD  GLU  31       0.420   7.977 -25.323  1.00 17.60
ATOM  146  OE1 GLU  31       0.071   8.535 -26.389  1.00 17.60
ATOM  147  OE2 GLU  31       0.224   6.767 -25.038  1.00 17.60
ATOM  148  C   GLU  31       0.977  11.856 -22.225  1.00 17.60
ATOM  149  O   GLU  31       1.617  12.709 -22.862  1.00 17.60
ATOM  150  N   ASP  32      -0.020  12.135 -21.374  1.00 17.60
ATOM  151  CA  ASP  32      -0.380  13.519 -21.120  1.00 17.60
ATOM  152  CB  ASP  32      -1.806  13.876 -21.385  1.00 17.60
ATOM  153  CG  ASP  32      -2.383  13.211 -22.630  1.00 17.60
ATOM  154  OD1 ASP  32      -1.715  13.229 -23.685  1.00 17.60
ATOM  155  OD2 ASP  32      -3.513  12.686 -22.528  1.00 17.60
ATOM  156  C   ASP  32      -0.224  13.515 -19.649  1.00 17.60
ATOM  157  O   ASP  32      -1.090  13.026 -18.936  1.00 17.60
ATOM  158  N   PRO  33       0.963  13.902 -19.215  1.00 17.60
ATOM  159  CD  PRO  33       2.250  13.686 -19.880  1.00 17.60
ATOM  160  CA  PRO  33       1.194  14.234 -17.839  1.00 17.60
ATOM  161  CB  PRO  33       2.739  14.198 -17.767  1.00 17.60
ATOM  162  CG  PRO  33       3.186  14.611 -19.154  1.00 17.60
ATOM  163  C   PRO  33       0.521  15.528 -17.360  1.00 17.60
ATOM  164  O   PRO  33       0.012  16.322 -18.173  1.00 17.60
ATOM  165  N   SER  34       0.535  15.659 -16.013  1.00 17.60
ATOM  166  CA  SER  34       0.072  16.832 -15.310  1.00 17.60
ATOM  167  CB  SER  34      -0.516  16.425 -13.995  1.00 17.60
ATOM  168  OG  SER  34      -1.502  15.451 -14.263  1.00 17.60
ATOM  169  C   SER  34       1.224  17.806 -15.065  1.00 17.60
ATOM  170  O   SER  34       2.367  17.445 -14.841  1.00 17.60
ATOM  171  N   GLN  35       0.863  19.075 -15.089  1.00 17.60
ATOM  172  CA  GLN  35       1.832  20.127 -14.999  1.00 17.60
ATOM  173  CB  GLN  35       1.510  21.138 -16.155  1.00 17.60
ATOM  174  CG  GLN  35       2.298  21.021 -17.486  1.00 17.60
ATOM  175  CD  GLN  35       3.828  21.101 -17.327  1.00 17.60
ATOM  176  OE1 GLN  35       4.570  20.435 -18.044  1.00 17.60
ATOM  177  NE2 GLN  35       4.389  21.893 -16.433  1.00 17.60
ATOM  178  C   GLN  35       1.772  20.757 -13.592  1.00 17.60
ATOM  179  O   GLN  35       2.032  20.065 -12.593  1.00 17.60
ATOM  180  N   ASN  36       1.362  22.041 -13.470  1.00 17.60
ATOM  181  CA  ASN  36       1.316  22.717 -12.188  1.00 17.60
ATOM  182  CB  ASN  36       1.963  24.116 -12.270  1.00 17.60
ATOM  183  CG  ASN  36       3.389  24.150 -11.671  1.00 17.60
ATOM  184  OD1 ASN  36       3.695  25.022 -10.844  1.00 17.60
ATOM  185  ND2 ASN  36       4.332  23.267 -12.005  1.00 17.60
ATOM  186  C   ASN  36      -0.121  22.852 -11.741  1.00 17.60
ATOM  187  O   ASN  36      -0.850  23.796 -12.035  1.00 17.60
ATOM  188  N   THR  37      -0.429  21.720 -11.128  1.00 17.60
ATOM  189  CA  THR  37      -1.650  21.381 -10.443  1.00 17.60
ATOM  190  CB  THR  37      -1.625  19.938  -9.989  1.00 17.60
ATOM  191  OG1 THR  37      -1.226  19.085 -11.071  1.00 17.60
ATOM  192  CG2 THR  37      -2.993  19.553  -9.497  1.00 17.60
ATOM  193  C   THR  37      -1.725  22.256  -9.221  1.00 17.60
ATOM  196  O   THR  37      -2.481  23.203  -9.315  1.00 17.60
ATOM  195  N   ALA  38      -1.009  22.080  -8.107  1.00 17.60
ATOM  196  CA  ALA  38      -1.278  22.965  -6.989  1.00 17.60
ATOM  197  CB  ALA  38      -1.037  22.231  -5.708  1.00 17.60
ATOM  198  C   ALA  38      -0.469  24.243  -6.977  1.00 17.60
ATOM  199  O   ALA  38       0.131  24.564  -7.997  1.00 17.60
ATOM  200  N   GLN  39      -0.399  25.033  -5.897  1.00 17.60
ATOM  201  CA  GLN  39       0.532  26.157  -5.813  1.00 17.60
ATOM  202  CB  GLN  39      -0.171  27.351  -6.332  1.00 17.60
ATOM  203  CG  GLN  39       0.431  28.749  -6.308  1.00 17.60
ATOM  204  CD  GLN  39      -0.728  29.737  -6.491  1.00 17.60
ATOM  205  OE1 GLN  39      -1.061  30.597  -5.656  1.00 17.60
ATOM  206  NE2 GLN  39      -1.418  29.563  -7.636  1.00 17.60
ATOM  207  C   GLN  39       0.904  26.284  -4.331  1.00 17.60
ATOM  208  O   GLN  39       0.064  26.148  -3.429  1.00 17.60
ATOM  209  N   LEU  40       2.186  26.560  -4.057  1.00 17.60
ATOM  210  CA  LEU  40       2.791  26.451  -2.705  1.00 17.60
ATOM  211  CB  LEU  40       6.200  27.087  -2.926  1.00 17.60
ATOM  212  CG  LEU  40       5.404  26.933  -2.007  1.00 17.60
ATOM  213  CD1 LEU  40       5.689  28.318  -1.462  1.00 17.60
ATOM  214  CD2 LEU  40       5.196  25.882  -0.934  1.00 17.60
ATOM  215  C   LEU  40       2.027  26.986  -1.454  1.00 17.60
ATOM  216  O   LEU  40       1.587  26.281  -0.549  1.00 17.60
ATOM  217  N   ASP  41       1.719  28.259  -1.672  1.00 17.60
ATOM  218  CA  ASP  41       1.042  29.206  -0.839  1.00 17.60
ATOM  219  CB  ASP  41       0.821  30.436  -1.716  1.00 17.60
ATOM  220  CG  ASP  41      -0.499  30.564  -2.545  1.00 17.60
ATOM  221  OD1 ASP  41      -0.940  31.725  -2.738  1.00 17.60
ATOM  222  OD2 ASP  41      -1.104  29.553  -2.975  1.00 17.60
ATOM  223  C   ASP  41      -0.253  28.734  -0.247  1.00 17.60
ATOM  224  O   ASP  41      -0.808  29.339   0.671  1.00 17.60
ATOM  225  N   GLN  42      -0.807  27.741  -0.880  1.00 17.60
ATOM  226  CA  GLN  42      -2.056  27.326  -0.376  1.00 17.60
ATOM  227  CB  GLN  42      -2.919  27.329  -1.577  1.00 17.60
ATOM  228  CG  GLN  42      -2.650  25.992  -2.512  1.00 17.60
ATOM  229  CD  GLN  42      -2.803  26.370  -3.970  1.00 17.60
ATOM  230  OE1 GLN  42      -2.446  27.439  -4.418  1.00 17.60
ATOM  231  NE2 GLN  42      -3.557  25.530  -4.782  1.00 17.60
ATOM  232  C   GLN  42      -2.001  26.115   0.529  1.00 17.60
ATOM  233  O   GLN  42      -3.041  25.511   0.823  1.00 17.60
ATOM  234  N   PHE  43      -0.796  25.784   0.981  1.00 17.60
ATOM  235  CA  PHE  43      -0.521  24.696   1.881  1.00 17.60
ATOM  236  CB  PHE  43       0.476  23.683   1.316  1.00 17.60
ATOM  237  CG  PHE  43      -0.091  22.886   0.147  1.00 17.60
ATOM  238  CD1 PHE  43      -0.848  21.783   0.389  1.00 17.60
ATOM  239  CD2 PHE  43       0.090  23.337  -1.126  1.00 17.60
ATOM  240  CE1 PHE  43      -1.434  21.143  -0.646  1.00 17.60
ATOM  241  CE2 PHE  43      -0.508  22.676  -2.157  1.00 17.60
ATOM  242  CZ  PHE  43      -1.271  21.585  -1.922  1.00 17.60
ATOM  243  C   PHE  43       0.158  25.400   2.984  1.00 17.60
ATOM  244  O   PHE  43       1.028  26.258   2.767  1.00 17.60
ATOM  245  N   ASP  44      -0.285  25.003   4.166  1.00 17.60
ATOM  246  CA  ASP  44       0.297  25.522   5.395  1.00 17.60
ATOM  247  CB  ASP  44      -0.777  25.931   6.353  1.00 17.60
ATOM  248  CG  ASP  44      -0.387  27.241   7.069  1.00 17.60
ATOM  249  OD1 ASP  44      -0.497  27.262   8.308  1.00 17.60
ATOM  250  OD2 ASP  44       0.018  28.246   6.433  1.00 17.60
ATOM  251  C   ASP  44       1.042  24.327   5.901  1.00 17.60
ATOM  252  O   ASP  44       0.446  23.234   5.854  1.00 17.60
ATOM  253  N   ARG  45       2.309  24.508   6.329  1.00 17.60
ATOM  254  CA  ARG  45       3.337  23.576   6.654  1.00 17.60
ATOM  255  CB  ARG  45       4.671  23.962   5.952  1.00 17.60
ATOM  256  CG  ARG  45       5.807  24.822   6.586  1.00 17.60
ATOM  257  CD  ARG  45       6.831  24.063   7.474  1.00 17.60
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ATOM	258	NE	ARG	45	8.189	24.601	7.476	1.00	17.60
ATOM	259	CZ	ARG	45	8.709	25.370	8.477	1.00	17.60
ATOM	260	NH1	ARG	45	8.021	25.738	9.585	1.00	17.60
ATOM	261	NH2	ARG	45	10.007	25.735	8.433	1.00	17.60
ATOM	262	C	ARG	45	3.703	23.196	8.089	1.00	17.60
ATOM	263	O	ARG	45	4.185	24.057	8.839	1.00	17.60
ATOM	264	N	ILE	46	3.597	21.883	8.436	1.00	17.60
ATOM	265	CA	ILE	46	3.794	21.479	9.789	1.00	17.60
ATOM	266	CB	ILE	46	2.821	20.312	10.090	1.00	17.60
ATOM	267	CG2	ILE	46	2.873	20.139	11.594	1.00	17.60
ATOM	268	CG1	ILE	46	1.380	20.590	9.628	1.00	17.60
ATOM	269	CD1	ILE	46	0.690	21.965	9.979	1.00	17.60
ATOM	270	C	ILE	46	5.211	20.974	10.073	1.00	17.60
ATOM	271	O	ILE	46	5.986	21.715	10.597	1.00	17.60
ATOM	272	N	LYS	47	5.659	19.766	9.765	1.00	17.60
ATOM	273	CA	LYS	47	7.014	19.387	10.146	1.00	17.60
ATOM	274	CB	LYS	47	7.072	18.778	11.591	1.00	17.60
ATOM	275	CG	LYS	47	6.566	17.394	12.064	1.00	17.60
ATOM	276	CD	LYS	47	7.572	16.224	12.313	1.00	17.60
ATOM	277	CE	LYS	47	8.029	16.390	13.239	1.00	17.60
ATOM	278	NZ	LYS	47	10.045	16.059	12.546	1.00	17.60
ATOM	279	C	LYS	47	7.571	18.370	9.177	1.00	17.60
ATOM	280	O	LYS	47	6.837	17.729	8.625	1.00	17.60
ATOM	281	N	THR	48	8.880	18.210	9.284	1.00	17.60
ATOM	282	CA	THR	48	9.671	17.302	8.501	1.00	17.60
ATOM	283	CB	THR	48	11.026	17.985	8.610	1.00	17.60
ATOM	284	OG1	THR	48	10.787	19.207	8.034	1.00	17.60
ATOM	285	CG2	THR	48	12.152	17.122	7.984	1.00	17.60
ATOM	286	C	THR	48	9.554	15.860	8.948	1.00	17.60
ATOM	287		THR	48	10.119	15.407	9.937	1.00	17.60
ATOM	288	N	LEU	49	8.679	15.197	8.233	1.00	17.60
ATOM	289	CA	LEU	49	8.601	13.821	8.449	1.00	17.60
ATOM	290	CB	LEU	49	7.338	13.369	7.512	1.00	17.60
ATOM	291	CG	LEU	49	5.952	13.869	7.766	1.00	17.60
ATOM	292	CD1	LEU	49	5.078	13.387	6.647	1.00	17.60
ATOM	293	CD2	LEU	49	5.429	13.371	9.097	1.00	17.60
ATOM	294	C	LEU	49	9.620	12.981	8.216	1.00	17.60
ATOM	295	O	LEU	49	9.935	12.123	9.052	1.00	17.60
ATOM	296	N	GLY	50	10.276	13.192	7.068	1.00	17.60
ATOM	297	CA	GLY	50	11.429	12.399	6.695	1.00	17.60
ATOM	298	C	GLY	50	12.442	13.264	5.988	1.00	17.60
ATOM	299	O	GLY	50	12.205	14.419	5.642	1.00	17.60
ATOM	300	N	THR	51	13.630	12.769	5.802	1.00	17.60
ATOM	301	CA	THR	51	14.560	13.512	5.000	1.00	17.60
ATOM	302	CB	THR	51	15.596	14.180	5.938	1.00	17.60
ATOM	303	OG1	THR	51	15.964	15.381	5.265	1.00	17.60
ATOM	304	CG2	THR	51	16.818	13.369	6.254	1.00	17.60
ATOM	305	C	THR	51	15.113	12.417	4.123	1.00	17.60
ATOM	306	O	THR	51	14.728	11.247	4.317	1.00	17.60
ATOM	307	N	GLY	52	15.958	12.762	3.145	1.00	17.60
ATOM	308	CA	GLY	52	16.599	11.722	2.295	1.00	17.60
ATOM	309	C	GLY	52	17.729	12.371	1.492	1.00	17.60
ATOM	310	O	GLY	52	17.903	13.550	1.819	1.00	17.60
ATOM	311	N	SER	53	18.538	11.807	0.556	1.00	17.60
ATOM	312	CA	SER	53	19.369	12.712	-0.211	1.00	17.60
ATOM	313	CB	SER	53	20.556	12.112	-0.777	1.00	17.60
ATOM	314	OG	SER	53	21.209	13.380	-0.990	1.00	17.60
ATOM	315	C	SER	53	18.599	13.241	-1.401	1.00	17.60
ATOM	316	O	SER	53	17.719	12.495	-1.808	1.00	17.60
ATOM	317	N	PHE	54	18.919	14.449	-1.964	1.00	17.60
ATOM	318	CA	PHE	54	18.231	15.267	-3.033	1.00	17.60
ATOM	319	CB	PHE	54	18.194	14.724	-4.518	1.00	17.60
ATOM	320	CG	PHE	54	18.455	13.239	-4.695	1.00	17.60
ATOM	321	CD1	PHE	54	19.751	12.765	-4.618	1.00	17.60
ATOM	322	CD2	PHE	54	17.397	12.367	-4.847	1.00	17.60
ATOM	323	CE1	PHE	54	19.985	11.398	-4.683	1.00	17.60
ATOM	324	CE2	PHE	54	17.650	11.003	-4.910	1.00	17.60
ATOM	325	CZ	PHE	54	18.941	10.502	-4.827	1.00	17.60
ATOM	326	C	PHE	54	16.767	15.469	-2.728	1.00	17.60
ATOM	327	O	PHE	54	16.282	16.596	-2.728	1.00	17.60
ATOM	328	N	GLY	55	16.100	14.348	-2.499	1.00	17.60
ATOM	329	CA	GLY	55	14.764	14.257	-1.950	1.00	17.60
ATOM	330	C	GLY	55	14.644	15.193	-0.761	1.00	17.60
ATOM	331	O	GLY	55	13.736	16.032	-0.631	1.00	17.60
ATOM	332	N	ARG	56	15.627	15.015	0.099	1.00	17.60
ATOM	333	CA	ARG	56	15.776	15.966	1.146	1.00	17.60
ATOM	334	CB	ARG	56	16.515	17.149	0.499	1.00	17.60
ATOM	335	CG	ARG	56	18.035	16.734	0.270	1.00	17.60
ATOM	336	CD	ARG	56	18.907	16.107	1.434	1.00	17.60
ATOM	337	NE	ARG	56	18.543	16.650	2.742	1.00	17.60
ATOM	338	CZ	ARG	56	18.964	16.231	3.935	1.00	17.60
ATOM	339	NH1	ARG	56	19.804	15.207	4.065	1.00	17.60
ATOM	340	NH2	ARG	56	18.545	16.918	5.021	1.00	17.60
ATOM	341	C	ARG	56	14.515	16.347	1.886	1.00	17.60
ATOM	342	O	ARG	56	13.833	15.387	2.189	1.00	17.60
ATOM	343	N	VAL	57	14.052	17.560	2.321	1.00	17.60
ATOM	344	CA	VAL	57	13.050	17.719	3.182	1.00	17.60
ATOM	345	CB	VAL	57	13.014	19.327	3.584	1.00	17.60
ATOM	346	CG1	VAL	57	12.188	20.277	2.663	1.00	17.60
ATOM	347	CG2	VAL	57	12.402	19.422	4.949	1.00	17.60
ATOM	348	C	VAL	57	11.713	17.091	2.732	1.00	17.60
ATOM	349	O	VAL	57	11.420	16.901	1.534	1.00	17.60
ATOM	350	N	MET	58	10.950	16.665	3.746	1.00	17.60
ATOM	351	CA	MET	58	9.680	15.995	3.532	1.00	17.60
ATOM	352	CB	MET	58	10.129	14.616	3.336	1.00	17.60
ATOM	353	CG	MET	58	9.488	14.217	2.096	1.00	17.60
ATOM	354	SD	MET	58	8.148	13.359	2.895	1.00	17.60
ATOM	355	CE	MET	58	9.092	11.853	3.020	1.00	17.60
ATOM	356	C	MET	58	8.759	16.257	4.733	1.00	17.60
ATOM	357	O	MET	58	8.716	15.559	5.741	1.00	17.60
ATOM	358	N	LEU	59	8.076	17.374	4.566	1.00	17.60
ATOM	359	CA	LEU	59	7.269	18.051	5.512	1.00	17.60
ATOM	360	CB	LEU	59	7.270	19.543	5.146	1.00	17.60
ATOM	361	CG	LEU	59	8.353	20.548	4.697	1.00	17.60
ATOM	362	CD1	LEU	59	7.624	21.728	4.178	1.00	17.60
ATOM	363	CD2	LEU	59	9.230	21.069	5.801	1.00	17.60
ATOM	364	C	LEU	59	5.828	17.552	5.497	1.00	17.60
ATOM	365	O	LEU	59	5.327	17.479	4.370	1.00	17.60
ATOM	366	N	VAL	60	5.054	17.225	6.552	1.00	17.60
ATOM	367	CA	VAL	60	3.596	17.017	6.466	1.00	17.60
ATOM	368	CB	VAL	60	2.873	16.300	7.754	1.00	17.60
ATOM	369	CG1	VAL	60	3.013	17.069	9.050	1.00	17.60
ATOM	370	CG2	VAL	60	1.366	16.200	7.569	1.00	17.60
ATOM	371	C	VAL	60	3.044	18.408	6.375	1.00	17.60
ATOM	372	O	VAL	60	3.602	19.330	6.979	1.00	17.60
ATOM	373	N	LYS	61	2.001	18.629	5.601	1.00	17.60
ATOM	374	CA	LYS	61	1.271	19.886	5.690	1.00	17.60
ATOM	375	CB	LYS	61	1.586	20.885	4.567	1.00	17.60
ATOM	376	CG	LYS	61	2.742	20.749	3.692	1.00	17.60
ATOM	377	CD	LYS	61	2.378	19.569	2.828	1.00	17.60
ATOM	378	CE	LYS	61	1.016	19.519	2.112	1.00	17.60
ATOM	379	NZ	LYS	61	-0.132	19.201	2.962	1.00	17.60
ATOM	380	C	LYS	61	-0.253	19.682	5.695	1.00	17.60
ATOM	381	O	LYS	61	-0.782	18.584	5.959	1.00	17.60
ATOM	382	N	HIS	62	-0.993	20.743	5.432	1.00	17.60
ATOM	383	CA	HIS	62	-2.415	20.832	5.610	1.00	17.60
ATOM	384	CB	HIS	62	-2.705	21.658	6.769	1.00	17.60
ATOM	385	CG	HIS	62	-4.039	21.721	7.497	1.00	17.60
ATOM	386	CD2	HIS	62	-4.267	22.732	8.463	1.00	17.60
ATOM	387	ND1	HIS	62	-5.125	20.915	7.576	1.00	17.60

ATOM	388	CE1	HIS	62	-5.957	21.388	8.522	1.00	17.60
ATOM	389	NE2	HIS	62	-5.431	22.491	9.044	1.00	17.60
ATOM	390	C	HIS	62	-2.588	21.690	6.437	1.00	17.60
ATOM	391	O	HIS	62	-1.861	22.678	6.233	1.00	17.60
ATOM	392	N	LYS	63	-3.452	21.170	5.615	1.00	17.60
ATOM	393	CA	LYS	63	-4.021	21.905	2.508	1.00	17.60
ATOM	394	CB	LYS	63	-4.988	21.055	1.707	1.00	17.60
ATOM	395	CG	LYS	63	-5.893	21.854	0.736	1.00	17.60
ATOM	396	CD	LYS	63	-5.749	21.202	-0.598	1.00	17.60
ATOM	397	CE	LYS	63	-5.648	22.261	-1.616	1.00	17.60
ATOM	398	NZ	LYS	63	-4.632	23.198	-1.235	1.00	17.60
ATOM	399	C	LYS	63	-4.836	22.931	3.236	1.00	17.60
ATOM	400	O	LYS	63	-5.608	22.468	4.093	1.00	17.60
ATOM	401	N	GLU	64	-4.809	24.235	2.942	1.00	17.60
ATOM	402	CA	GLU	64	-5.653	25.218	3.629	1.00	17.60
ATOM	403	CB	GLU	64	-5.235	26.666	3.137	1.00	17.60
ATOM	404	CG	GLU	64	-3.724	27.045	3.392	1.00	17.60
ATOM	405	CD	GLU	64	-3.314	28.509	3.676	1.00	17.60
ATOM	406	OE1	GLU	64	-4.059	29.162	4.418	1.00	17.60
TOM	407	OE2	GLU	64	-2.265	29.002	3.198	1.00	17.60
.TOM	408	C	GLU	64	-7.175	24.965	3.454	1.00	17.60
ATOM	409	O	GLU	64	-7.960	25.886	3.663	1.00	17.60
ATOM	410	N	SER	65	-7.664	23.748	3.079	1.00	17.60
ATOM	411	CA	SER	65	-9.057	23.326	3.010	1.00	17.60
ATOM	412	CB	SER	65	-9.613	23.537	1.638	1.00	17.60
ATOM	413	OG	SER	65	-9.657	24.945	1.394	1.00	17.60
ATOM	414	C	SER	65	-9.251	21.876	3.406	1.00	17.60
ATOM	415	O	SER	65	-9.735	20.999	2.697	1.00	17.60
ATOM	416	N	GLY	66	-8.724	21.668	4.599	1.00	17.60
ATOM	417	CA	GLY	66	-9.009	20.469	5.313	1.00	17.60
ATOM	418	C	GLY	66	-7.841	19.560	5.575	1.00	17.60
ATOM	419	O	GLY	66	-7.280	19.461	6.670	1.00	17.60
ATOM	420	N	ASN	67	-7.443	18.993	4.465	1.00	17.60
ATOM	421	CA	ASN	67	-6.574	17.861	4.513	1.00	17.60
ATOM	422	CB	ASN	67	-6.651	17.021	3.255	1.00	17.60
ATOM	423	CG	ASN	67	-8.024	16.605	2.884	1.00	17.60
ATOM	424	OD1	ASN	67	-8.514	15.593	3.340	1.00	17.60
ATOM	425	ND2	ASN	67	-8.612	17.407	2.022	1.00	17.60
ATOM	426	C	ASN	67	-5.102	17.987	4.757	1.00	17.60
ATOM	427	O	ASN	67	-4.534	19.068	4.657	1.00	17.60
ATOM	428	N	HIS	68	-4.525	16.841	5.115	1.00	17.60
ATOM	429	CA	HIS	68	-3.105	16.720	5.349	1.00	17.60
ATOM	430	CB	HIS	68	-2.853	16.115	6.720	1.00	17.60
ATOM	431	CG	HIS	68	-3.156	17.072	7.865	1.00	17.60
TOM	432	CD2	HIS	68	-4.294	17.052	8.606	1.00	17.60
.TOM	433	ND1	HIS	68	-2.371	18.021	8.350	1.00	17.60
ATOM	434	CE1	HIS	68	-2.962	18.580	9.355	1.00	17.60
ATOM	435	NE2	HIS	68	-4.106	17.987	9.486	1.00	17.60
ATOM	436	C	HIS	68	-2.549	15.826	4.236	1.00	17.60
ATOM	437	O	HIS	68	-3.278	15.041	3.615	1.00	17.60
ATOM	438	N	TYR	69	-1.265	15.957	3.983	1.00	17.60
ATOM	439	CA	TYR	69	-0.622	15.375	2.843	1.00	17.60
ATOM	440	CB	TYR	69	-0.865	16.215	1.563	1.00	17.60
ATOM	441	CG	TYR	69	-2.254	16.372	0.908	1.00	17.60
ATOM	442	CD1	TYR	69	-3.013	15.273	0.628	1.00	17.60
ATOM	443	CE1	TYR	69	-4.267	15.413	0.077	1.00	17.60
ATOM	444	CD2	TYR	69	-2.766	17.629	0.606	1.00	17.60
ATOM	445	CE2	TYR	69	-4.018	17.783	0.056	1.00	17.60
ATOM	446	CZ	TYR	69	-4.779	16.657	-0.201	1.00	17.60
ATOM	447	OH	TYR	69	-6.104	16.750	-0.623	1.00	17.60
ATOM	448	C	TYR	69	0.862	15.452	3.207	1.00	17.60
ATOM	449	O	TYR	69	1.211	15.956	4.268	1.00	17.60
ATOM	450	N	ALA	70	1.793	14.986	2.390	1.00	17.60
ATOM	451	CA	ALA	70	3.197	15.038	2.711	1.00	17.60
ATOM	452	CB	ALA	70	3.730	13.630	2.746	1.00	17.60
ATOM	453	C	ALA	70	3.783	15.795	1.533	1.00	17.60
ATOM	454	O	ALA	70	3.437	15.320	0.450	1.00	17.60
ATOM	455	N	MET	71	4.548	16.909	1.586	1.00	17.60
ATOM	456	CA	MET	71	5.139	17.483	0.365	1.00	17.60
ATOM	457	CB	MET	71	5.202	18.987	0.401	1.00	17.60
ATOM	458	CG	MET	71	4.212	19.775	-0.256	1.00	17.60
ATOM	459	SD	MET	71	4.873	21.446	-0.425	1.00	17.60
ATOM	460	CE	MET	71	3.859	22.475	0.586	1.00	17.60
ATOM	461	C	MET	71	6.566	16.969	0.125	1.00	17.60
ATOM	462	O	MET	71	7.301	16.966	1.121	1.00	17.60
ATOM	463	N	LYS	72	7.069	16.516	-1.051	1.00	17.60
ATOM	464	CA	LYS	72	8.474	16.136	-1.230	1.00	17.60
ATOM	465	CB	LYS	72	8.639	14.971	-2.188	1.00	17.60
ATOM	466	CG	LYS	72	9.921	14.141	-2.247	1.00	17.60
ATOM	467	CD	LYS	72	9.686	13.128	-3.350	1.00	17.60
ATOM	468	CE	LYS	72	10.693	12.015	-3.314	1.00	17.60
ATOM	469	NZ	LYS	72	11.931	12.403	-3.932	1.00	17.60
ATOM	470	C	LYS	72	9.038	17.379	-1.867	1.00	17.60
ATOM	471	O	LYS	72	8.510	17.864	-2.872	1.00	17.60
ATOM	472	N	ILE	73	10.064	17.973	-1.325	1.00	17.60
ATOM	473	CA	ILE	73	10.516	19.214	-1.851	1.00	17.60
ATOM	474	CB	ILE	73	10.552	20.295	-0.782	1.00	17.60
ATOM	475	CG2	ILE	73	10.818	21.641	-1.462	1.00	17.60
ATOM	476	CG1	ILE	73	9.201	20.263	0.036	1.00	17.60
ATOM	477	CD1	ILE	73	9.227	21.445	0.988	1.00	17.60
ATOM	478	C	ILE	73	11.921	18.870	-2.232	1.00	17.60
ATOM	479	O	ILE	73	12.721	18.747	-1.293	1.00	17.60
ATOM	480	N	LEU	74	12.139	18.696	-3.561	1.00	17.60
ATOM	481	CA	LEU	74	13.427	18.498	-4.269	1.00	17.60
ATOM	482	CB	LEU	74	13.316	17.822	-5.623	1.00	17.60
ATOM	483	CG	LEU	74	13.044	16.409	-5.844	1.00	17.60
ATOM	484	CD1	LEU	74	14.154	15.722	-5.168	1.00	17.60
ATOM	485	CD2	LEU	74	11.732	15.967	-5.291	1.00	17.60
ATOM	486	C	LEU	74	14.024	19.854	-4.616	1.00	17.60
ATOM	487	O	LEU	74	13.371	20.722	-5.203	1.00	17.60
ATOM	488	N	ASP	75	15.294	20.063	-4.358	1.00	17.60
ATOM	489	CA	ASP	75	15.864	21.384	-4.577	1.00	17.60
ATOM	490	CB	ASP	75	17.023	21.597	-3.561	1.00	17.60
ATOM	491	CG	ASP	75	17.847	22.892	-3.653	1.00	17.60
ATOM	492	OD1	ASP	75	18.303	23.194	-4.748	1.00	17.60
ATOM	493	OD2	ASP	75	18.046	23.592	-2.647	1.00	17.60
ATOM	494	C	ASP	75	16.349	21.356	-5.996	1.00	17.60
ATOM	495	O	ASP	75	17.334	20.626	-6.189	1.00	17.60
ATOM	496	N	LYS	76	15.812	22.105	-6.962	1.00	17.60
ATOM	497	CA	LYS	76	16.296	21.980	-8.344	1.00	17.60
ATOM	498	CB	LYS	76	15.825	23.151	-9.221	1.00	17.60
ATOM	499	CG	LYS	76	14.393	22.951	-9.711	1.00	17.60
ATOM	500	CD	LYS	76	13.857	23.988	-10.680	1.00	17.60
ATOM	501	CE	LYS	76	14.099	25.407	-10.127	1.00	17.60
ATOM	502	NZ	LYS	76	13.055	26.340	-10.483	1.00	17.60
ATOM	503	C	LYS	76	17.870	21.864	-8.522	1.00	17.60
ATOM	504	O	LYS	76	18.241	20.886	-9.139	1.00	17.60
ATOM	505	N	GLN	77	18.665	22.716	-7.856	1.00	17.60
ATOM	506	CA	GLN	77	20.154	22.762	-7.969	1.00	17.60
ATOM	507	CB	GLN	77	20.883	23.889	-7.223	1.00	17.60
ATOM	508	CG	GLN	77	20.007	25.074	-6.942	1.00	17.60
ATOM	509	CD	GLN	77	20.651	26.417	-7.186	1.00	17.60
ATOM	510	OE1	GLN	77	21.571	26.605	-7.972	1.00	17.60
ATOM	511	NE2	GLN	77	20.096	27.405	-6.518	1.00	17.60
ATOM	512	C	GLN	77	20.803	21.534	-7.396	1.00	17.60
ATOM	513	O	GLN	77	21.516	20.883	-8.161	1.00	17.60
ATOM	514	N	LYS	78	20.549	21.139	-6.137	1.00	17.60
ATOM	515	CA	LYS	78	21.231	19.971	-5.634	1.00	17.60
ATOM	516	CB	LYS	78	20.955	19.832	-4.154	1.00	17.60
ATOM	517	CG	LYS	78	19.878	19.027	-3.541	1.00	17.60

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ATOM  518  CD  LYS  78      19.876  19.183  -1.976  1.00 17.60
ATOM  519  CE  LYS  78      20.979  18.494  -1.095  1.00 17.60
ATOM  520  NZ  LYS  78      21.011  17.008  -1.167  1.00 17.60
ATOM  521  C   LYS  78      20.860  18.726  -6.414  1.00 17.60
ATOM  522  O   LYS  78      21.716  17.854  -6.553  1.00 17.60
ATOM  523  N   VAL  79      19.663  18.686  -7.045  1.00 17.60
ATOM  524  CA  VAL  79      19.252  17.606  -7.975  1.00 17.60
ATOM  525  CB  VAL  79      17.707  17.750  -8.319  1.00 17.60
ATOM  526  CG1 VAL  79      17.391  17.194  -9.668  1.00 17.60
ATOM  527  CG2 VAL  79      16.848  16.770  -7.535  1.00 17.60
ATOM  528  C   VAL  79      20.114  17.607  -9.266  1.00 17.60
ATOM  529  O   VAL  79      20.471  16.533  -9.797  1.00 17.60
ATOM  530  N   VAL  80      20.485  18.791  -9.782  1.00 17.60
ATOM  531  CA  VAL  80      21.324  18.929 -10.965  1.00 17.60
ATOM  532  CB  VAL  80      21.236  20.402 -11.533  1.00 17.60
ATOM  533  CG1 VAL  80      22.059  20.499 -12.782  1.00 17.60
ATOM  534  CG2 VAL  80      19.830  20.793 -11.975  1.00 17.60
ATOM  535  C   VAL  80      22.736  18.571 -10.523  1.00 17.60
ATOM  536  O   VAL  80      23.460  17.913 -11.246  1.00 17.60
ATOM  537  N   LYS  81      23.104  18.899  -9.292  1.00 17.60
ATOM  538  CA  LYS  81      24.419  18.569  -8.795  1.00 17.60
ATOM  539  CB  LYS  81      24.585  18.959  -7.302  1.00 17.60
ATOM  540  CG  LYS  81      25.391  20.214  -7.164  1.00 17.60
ATOM  541  CD  LYS  81      24.710  21.443  -7.699  1.00 17.60
ATOM  542  CE  LYS  81      25.375  22.618  -7.033  1.00 17.60
ATOM  543  NZ  LYS  81      25.193  22.570  -5.601  1.00 17.60
ATOM  544  C   LYS  81      24.702  17.095  -8.823  1.00 17.60
ATOM  545      LYS  81      25.718  16.641  -9.330  1.00 17.60
ATOM  546  N   LEU  82      23.733  16.391  -8.226  1.00 17.60
ATOM  547  CA  LEU  82      23.799  14.971  -7.988  1.00 17.60
ATOM  548  CB  LEU  82      22.905  14.670  -6.779  1.00 17.60
ATOM  549  CG  LEU  82      23.361  14.917  -5.312  1.00 17.60
ATOM  550  CD1 LEU  82      24.485  15.939  -5.147  1.00 17.60
ATOM  551  CD2 LEU  82      22.179  15.530  -4.583  1.00 17.60
ATOM  552  C   LEU  82      23.450  14.132  -9.200  1.00 17.60
ATOM  553  O   LEU  82      23.467  12.908  -9.132  1.00 17.60
ATOM  554  N   LYS  83      23.254  14.747 -10.373  1.00 17.60
ATOM  555  CA  LYS  83      23.054  14.042 -11.657  1.00 17.60
ATOM  556  CB  LYS  83      24.152  12.946 -11.886  1.00 17.60
ATOM  557  CG  LYS  83      25.634  13.326 -11.937  1.00 17.60
ATOM  558  CD  LYS  83      26.578  12.089 -12.059  1.00 17.60
ATOM  559  CE  LYS  83      28.102  12.495 -12.088  1.00 17.60
ATOM  560  NZ  LYS  83      29.068  11.417 -12.425  1.00 17.60
ATOM  561  C   LYS  83      21.666  13.372 -11.713  1.00 17.60
ATOM  562  O   LYS  83      21.434  12.382 -12.454  1.00 17.60
ATOM  563  N   GLN  84      20.667  13.902 -10.968  1.00 17.60
ATOM  564  CA  GLN  84      19.411  13.182 -10.969  1.00 17.60
ATOM  565  CB  GLN  84      19.057  12.853  -9.552  1.00 17.60
ATOM  566  CG  GLN  84      20.176  12.285  -8.669  1.00 17.60
ATOM  567  CD  GLN  84      20.643  10.889  -9.024  1.00 17.60
ATOM  568  OE1 GLN  84      19.874   9.960  -9.305  1.00 17.60
ATOM  569  NE2 GLN  84      21.937  10.672  -9.091  1.00 17.60
ATOM  570  C   GLN  84      18.278  13.934 -11.632  1.00 17.60
ATOM  571  O   GLN  84      17.109  13.778 -11.279  1.00 17.60
ATOM  572  N   ILE  85      18.600  14.687 -12.697  1.00 17.60
ATOM  573  CA  ILE  85      17.640  15.538 -13.386  1.00 17.60
ATOM  574  CB  ILE  85      18.270  16.451 -14.485  1.00 17.60
ATOM  575  CG2 ILE  85      17.366  17.670 -14.615  1.00 17.60
ATOM  576  CG1 ILE  85      19.632  17.002 -14.126  1.00 17.60
ATOM  577  CD1 ILE  85      20.096  18.302 -14.805  1.00 17.60
ATOM  578  C   ILE  85      16.699  14.560 -14.034  1.00 17.60
ATOM  579  O   ILE  85      15.520  14.563 -13.681  1.00 17.60
ATOM  580  N   GLU  86      17.201  13.605 -14.834  1.00 17.60
ATOM  581  CA  GLU  86      16.276  12.693 -15.466  1.00 17.60
ATOM  582  CB  GLU  86      17.007  11.795 -16.474  1.00 17.60
ATOM  583  CG  GLU  86      16.041  10.985 -17.407  1.00 17.60
ATOM  584  CD  GLU  86      15.076  11.726 -18.374  1.00 17.60
ATOM  585  OE1 GLU  86      13.851  11.484 -18.384  1.00 17.60
ATOM  586  OE2 GLU  86      15.568  12.552 -19.136  1.00 17.60
ATOM  587  C   GLU  86      15.517  11.847 -16.443  1.00 17.60
ATOM  588  O   GLU  86      14.288  11.783 -16.397  1.00 17.60
ATOM  589  N   HIS  87      16.035  11.259 -13.338  1.00 17.60
ATOM  590  CA  HIS  87      15.113  10.446 -12.532  1.00 17.60
ATOM  591  CB  HIS  87      15.727   9.448 -11.537  1.00 17.60
ATOM  592  CG  HIS  87      17.003   8.641 -11.858  1.00 17.60
ATOM  593  CD2 HIS  87      18.119   8.826 -11.108  1.00 17.60
ATOM  594  ND1 HIS  87      17.327   7.679 -12.711  1.00 17.60
ATOM  595  CE1 HIS  87      18.551   7.308 -12.496  1.00 17.60
ATOM  596  NE2 HIS  87      19.012   8.005 -11.528  1.00 17.60
ATOM  597  C   HIS  87      14.252  11.361 -11.680  1.00 17.60
ATOM  598  O   HIS  87      13.380  10.833 -11.038  1.00 17.60
ATOM  599  N   THR  88      14.357  12.674 -11.612  1.00 17.60
ATOM  600  CA  THR  88      13.349  13.498 -10.954  1.00 17.60
ATOM  601  CB  THR  88      13.979  14.911 -10.816  1.00 17.60
ATOM  602  OG1 THR  88      14.995  14.896  -9.818  1.00 17.60
ATOM  603  CG2 THR  88      12.968  15.930 -10.465  1.00 17.60
ATOM  604  C   THR  88      12.065  13.494 -11.837  1.00 17.60
ATOM  605  O   THR  88      10.895  13.407 -11.455  1.00 17.60
ATOM  606  N   LEU  89      12.306  13.487 -13.118  1.00 17.60
ATOM  607  CA  LEU  89      11.311  13.632 -14.152  1.00 17.60
ATOM  608  CB  LEU  89      12.123  14.039 -15.377  1.00 17.60
ATOM  609  CG  LEU  89      12.826  15.444 -15.260  1.00 17.60
ATOM  610  CD1 LEU  89      13.869  15.545 -16.328  1.00 17.60
ATOM  611  CD2 LEU  89      11.816  16.591 -15.333  1.00 17.60
ATOM  612  C   LEU  89      10.482  12.615 -14.309  1.00 17.60
ATOM  613  O   LEU  89       9.275  12.529 -14.389  1.00 17.60
ATOM  614  N   ASN  90      11.141  11.270 -14.212  1.00 17.60
ATOM  615  CA  ASN  90      10.507   9.954 -14.227  1.00 17.60
ATOM  616  CB  ASN  90      11.395   8.734 -14.201  1.00 17.60
ATOM  617  CG  ASN  90      12.357   8.498 -15.338  1.00 17.60
ATOM  618  OD1 ASN  90      12.012   8.535 -16.514  1.00 17.60
ATOM  619  ND2 ASN  90      13.613   8.175 -15.045  1.00 17.60
ATOM  620  C   ASN  90       9.721   9.713 -12.976  1.00 17.60
ATOM  621  O   ASN  90       8.758   8.938 -13.048  1.00 17.60
ATOM  622  N   GLU  91      10.058  10.296 -11.819  1.00 17.60
ATOM  623  CA  GLU  91       9.221  10.000 -10.673  1.00 17.60
ATOM  624  CB  GLU  91       9.911  10.261  -9.359  1.00 17.60
ATOM  625  CG  GLU  91      10.200  11.651  -8.869  1.00 17.60
ATOM  626  CD  GLU  91      10.923  11.556  -7.524  1.00 17.60
ATOM  627  OE1 GLU  91      10.343  10.981  -6.599  1.00 17.60
ATOM  628  OE2 GLU  91      12.051  12.056  -7.444  1.00 17.60
ATOM  629  C   GLU  91       7.919  10.767 -10.643  1.00 17.60
ATOM  630  O   GLU  91       6.875  10.199 -10.290  1.00 17.60
ATOM  631  N   LYS  92       7.932  12.044 -11.035  1.00 17.60
ATOM  632  CA  LYS  92       6.681  12.753 -11.143  1.00 17.60
ATOM  633  CB  LYS  92       6.950  14.192 -11.402  1.00 17.60
ATOM  634  CG  LYS  92       5.691  14.995 -11.282  1.00 17.60
ATOM  635  CD  LYS  92       4.914  15.064 -12.603  1.00 17.60
ATOM  636  CE  LYS  92       5.262  16.238 -13.569  1.00 17.60
ATOM  637  NZ  LYS  92       4.611  16.062 -14.839  1.00 17.60
ATOM  638  C   LYS  92       5.929  12.119 -12.296  1.00 17.60
ATOM  639  O   LYS  92       4.761  11.807 -12.089  1.00 17.60
ATOM  640  N   ARG  93       6.462  11.860 -13.493  1.00 17.60
ATOM  641  CA  ARG  93       5.668  11.249 -14.566  1.00 17.60
ATOM  642  CB  ARG  93       6.568  11.160 -15.753  1.00 17.60
ATOM  643  CG  ARG  93       5.876  11.035 -17.112  1.00 17.60
ATOM  644  CD  ARG  93       6.844  11.306 -18.281  1.00 17.60
ATOM  645  NE  ARG  93       6.085  11.232 -19.523  1.00 17.60
ATOM  646  CZ  ARG  93       6.594  10.762 -20.661  1.00 17.60
ATOM  647  NH1 ARG  93       7.854  10.330 -20.727  1.00 17.60
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ATOM	648	NH2	ARG	93	5.798	10.727	-21.725	1.00	17.60
ATOM	649	C	ARG	93	5.023	9.886	-14.274	1.00	17.60
ATOM	650	O	ARG	93	3.836	9.591	-14.540	1.00	17.60
ATOM	651	N	ILE	94	5.830	9.043	-13.661	1.00	17.60
ATOM	652	CA	ILE	94	5.297	7.759	-13.306	1.00	17.60
ATOM	653	CB	ILE	94	6.456	6.789	-12.958	1.00	17.60
ATOM	654	CG2	ILE	94	5.885	5.467	-12.409	1.00	17.60
ATOM	655	CG1	ILE	94	7.323	6.569	-14.191	1.00	17.60
ATOM	656	CD1	ILE	94	8.580	5.756	-13.815	1.00	17.60
ATOM	657	C	ILE	94	4.368	7.963	-12.117	1.00	17.60
ATOM	658	O	ILE	94	3.251	7.448	-12.383	1.00	17.60
ATOM	659	N	LEU	95	4.685	8.709	-11.052	1.00	17.60
ATOM	660	CA	LEU	95	3.739	8.785	-9.957	1.00	17.60
ATOM	661	CB	LEU	95	4.372	9.502	-8.745	1.00	17.60
ATOM	662	CG	LEU	95	5.054	8.546	-7.735	1.00	17.60
ATOM	663	CD1	LEU	95	5.654	9.364	-6.612	1.00	17.60
ATOM	664	CD2	LEU	95	4.088	7.682	-6.922	1.00	17.60
ATOM	665	C	LEU	95	2.405	9.443	-10.333	1.00	17.60
ATOM	666	O	LEU	95	1.377	9.036	-9.792	1.00	17.60
ATOM	667	N	GLN	96	2.282	10.384	-11.261	1.00	17.60
ATOM	668	CA	GLN	96	0.971	10.898	-11.565	1.00	17.60
ATOM	669	CB	GLN	96	1.064	12.220	-12.306	1.00	17.60
ATOM	670	CG	GLN	96	1.996	12.334	-13.505	1.00	17.60
ATOM	671	CD	GLN	96	1.285	12.173	-14.849	1.00	17.60
ATOM	672	OE1	GLN	96	0.470	12.994	-15.297	1.00	17.60
ATOM	673	NE2	GLN	96	1.586	11.117	-15.571	1.00	17.60
ATOM	674	C	GLN	96	0.266	9.882	-12.401	1.00	17.60
ATOM	675	O	GLN	96	-0.945	9.794	-12.303	1.00	17.60
ATOM	676	N	ALA	97	0.944	9.068	-13.208	1.00	17.60
ATOM	677	CA	ALA	97	0.236	8.133	-14.059	1.00	17.60
ATOM	678	CB	ALA	97	1.120	7.900	-15.219	1.00	17.60
ATOM	679	C	ALA	97	-0.367	6.797	-13.436	1.00	17.60
ATOM	680	O	ALA	97	-1.067	6.090	-13.891	1.00	17.60
ATOM	681	N	VAL	98	0.532	6.343	-12.413	1.00	17.60
ATOM	682	CA	VAL	98	0.224	5.084	-11.792	1.00	17.60
ATOM	683	CB	VAL	98	1.547	4.775	-11.104	1.00	17.60
ATOM	684	CG1	VAL	98	1.770	5.565	-9.813	1.00	17.60
ATOM	685	CG2	VAL	98	1.545	3.320	-10.879	1.00	17.60
ATOM	686	C	VAL	98	-1.052	5.138	-10.868	1.00	17.60
ATOM	687	O	VAL	98	-1.586	6.199	-10.521	1.00	17.60
ATOM	688	N	ASN	99	-1.625	3.977	-10.516	1.00	17.60
ATOM	689	CA	ASN	99	-2.740	3.837	-9.555	1.00	17.60
ATOM	690	CB	ASN	99	-4.052	4.387	-10.136	1.00	17.60
ATOM	691	CG	ASN	99	-5.295	4.391	-9.222	1.00	17.60
ATOM	692	OD1	ASN	99	-6.191	5.225	-9.398	1.00	17.60
ATOM	693	ND2	ASN	99	-5.583	3.508	-8.264	1.00	17.60
ATOM	694	C	ASN	99	-2.924	2.343	-9.207	1.00	17.60
ATOM	695	O	ASN	99	-3.281	1.531	-10.063	1.00	17.60
ATOM	696	N	PHE	100	-2.679	1.959	-7.961	1.00	17.60
ATOM	697	CA	PHE	100	-2.796	0.599	-7.442	1.00	17.60
ATOM	698	CB	PHE	100	-1.481	-0.145	-7.771	1.00	17.60
ATOM	699	CG	PHE	100	-1.617	-1.662	-7.671	1.00	17.60
ATOM	700	CD1	PHE	100	-2.400	-2.350	-8.582	1.00	17.60
ATOM	701	CD2	PHE	100	-1.075	-2.337	-6.622	1.00	17.60
ATOM	702	CE1	PHE	100	-2.665	-3.687	-8.458	1.00	17.60
ATOM	703	CE2	PHE	100	-1.344	-3.687	-6.499	1.00	17.60
ATOM	704	CZ	PHE	100	-2.133	-4.361	-7.403	1.00	17.60
ATOM	705	C	PHE	100	-3.038	0.719	-5.909	1.00	17.60
ATOM	706	O	PHE	100	-2.635	1.746	-5.348	1.00	17.60
ATOM	707	N	PRO	101	-3.657	-0.211	-5.139	1.00	17.60
ATOM	708	CD	PRO	101	-4.307	-1.418	-5.637	1.00	17.60
ATOM	709	CA	PRO	101	-3.995	-0.087	-3.716	1.00	17.60
ATOM	710	CB	PRO	101	-4.813	-1.312	-3.411	1.00	17.60
ATOM	711	CG	PRO	101	-5.468	-1.633	-4.722	1.00	17.60
ATOM	712	C	PRO	101	-2.890	0.068	-2.677	1.00	17.60

ATOM	713	O	PRO	101	-3.173	0.442	-1.542	1.00	17.60
ATOM	714	N	PHE	102	-1.649	-0.293	-3.018	1.00	17.60
ATOM	715	CA	PHE	102	-0.506	-0.267	-2.125	1.00	17.60
ATOM	716	CB	PHE	102	0.056	-1.735	-1.957	1.00	17.60
ATOM	717	CG	PHE	102	-0.930	-2.916	-1.742	1.00	17.60
ATOM	718	CD1	PHE	102	-0.887	-4.019	-2.603	1.00	17.60
ATOM	719	CD2	PHE	102	-1.881	-2.933	-0.712	1.00	17.60
ATOM	720	CE1	PHE	102	-1.748	-5.095	-2.462	1.00	17.60
ATOM	721	CE2	PHE	102	-2.742	-4.022	-0.576	1.00	17.60
ATOM	722	CZ	PHE	102	-2.672	-5.092	-1.453	1.00	17.60
ATOM	723	C	PHE	102	0.543	0.693	-2.742	1.00	17.60
ATOM	724	O	PHE	102	1.742	0.472	-2.577	1.00	17.60
ATOM	725	N	LEU	103	0.247	1.750	-3.509	1.00	17.60
ATOM	726	CA	LEU	103	1.263	2.698	-3.944	1.00	17.60
ATOM	727	CB	LEU	103	1.315	2.916	-5.357	1.00	17.60
ATOM	728	CG	LEU	103	1.974	1.981	-6.197	1.00	17.60
ATOM	729	CD1	LEU	103	1.342	0.638	-6.145	1.00	17.60
ATOM	730	CD2	LEU	103	1.852	2.566	-7.571	1.00	17.60
ATOM	731	C	LEU	103	0.808	4.024	-3.418	1.00	17.60
ATOM	732	O	LEU	103	-0.401	4.127	-3.231	1.00	17.60
ATOM	733	N	VAL	104	1.574	5.080	-3.196	1.00	17.60
ATOM	734	CA	VAL	104	0.967	6.234	-2.575	1.00	17.60
ATOM	735	CB	VAL	104	1.836	6.750	-1.428	1.00	17.60
ATOM	736	CG1	VAL	104	3.194	7.227	-1.906	1.00	17.60
ATOM	737	CG2	VAL	104	1.040	7.855	-0.716	1.00	17.60
ATOM	738	C	VAL	104	0.786	7.262	-3.610	1.00	17.60
ATOM	739	O	VAL	104	1.716	7.596	-4.357	1.00	17.60
ATOM	740	N	LYS	105	-0.449	7.803	-3.568	1.00	17.60
ATOM	741	CA	LYS	105	-0.979	8.736	-4.569	1.00	17.60
ATOM	742	CB	LYS	105	-2.470	8.934	-4.328	1.00	17.60
ATOM	743	CG	LYS	105	-3.467	7.803	-4.596	1.00	17.60
ATOM	744	CD	LYS	105	-4.642	7.737	-3.554	1.00	17.60
ATOM	745	CE	LYS	105	-4.355	6.777	-2.332	1.00	17.60
ATOM	746	NZ	LYS	105	-4.578	5.335	-2.573	1.00	17.60
ATOM	747	C	LYS	105	-0.301	10.093	-4.564	1.00	17.60
ATOM	748	O	LYS	105	-0.028	10.626	-3.509	1.00	17.60
ATOM	749	N	LEU	106	-0.045	10.700	-5.701	1.00	17.60
ATOM	750	CA	LEU	106	0.580	11.991	-5.866	1.00	17.60
ATOM	751	CB	LEU	106	1.469	12.029	-7.115	1.00	17.60
ATOM	752	CG	LEU	106	2.062	13.324	-7.608	1.00	17.60
ATOM	753	CD1	LEU	106	2.821	13.915	-6.500	1.00	17.60
ATOM	754	CD2	LEU	106	3.015	13.124	-8.738	1.00	17.60
ATOM	755	C	LEU	106	-0.674	12.746	-6.115	1.00	17.60
ATOM	756	O	LEU	106	-1.284	12.451	-7.124	1.00	17.60
ATOM	757	N	GLU	107	-1.131	13.585	-5.196	1.00	17.60
ATOM	758	CA	GLU	107	-2.315	14.385	-5.404	1.00	17.60
ATOM	759	CB	GLU	107	-3.055	14.665	-4.107	1.00	17.60
ATOM	760	CG	GLU	107	-4.575	14.347	-4.166	1.00	17.60
ATOM	761	CD	GLU	107	-4.918	13.097	-3.311	1.00	17.60
ATOM	762	OE1	GLU	107	-4.594	13.105	-2.110	1.00	17.60
ATOM	763	OE2	GLU	107	-5.485	12.118	-3.864	1.00	17.60
ATOM	764	C	GLU	107	-2.032	15.721	-6.031	1.00	17.60
ATOM	765	O	GLU	107	-2.974	16.285	-6.561	1.00	17.60
ATOM	766	N	PHE	108	-0.861	16.330	-5.911	1.00	17.60
ATOM	767	CA	PHE	108	-0.535	17.542	-6.663	1.00	17.60
ATOM	768	CB	PHE	108	-0.806	18.845	-5.926	1.00	17.60
ATOM	769	CG	PHE	108	-2.106	18.954	-5.139	1.00	17.60
ATOM	770	CD1	PHE	108	-3.253	19.454	-5.737	1.00	17.60
ATOM	771	CD2	PHE	108	-2.153	18.516	-3.831	1.00	17.60
ATOM	772	CE1	PHE	108	-4.452	19.506	-5.030	1.00	17.60
ATOM	773	CE2	PHE	108	-3.343	18.571	-3.130	1.00	17.60
ATOM	774	CZ	PHE	108	-4.500	19.058	-3.715	1.00	17.60
ATOM	775	C	PHE	108	0.961	17.592	-7.003	1.00	17.60
ATOM	776	O	PHE	108	1.819	17.092	-6.272	1.00	17.60
ATOM	777	N	SER	109	1.297	18.190	-8.129	1.00	17.60

ATOM	778	CA	SER	109	2.655	18.365	-8.589	1.00	17.60
ATOM	779	CB	SER	109	2.842	17.597	-9.865	1.00	17.60
ATOM	780	OG	SER	109	4.217	17.409	-10.103	1.00	17.60
ATOM	781	C	SER	109	2.706	19.857	-8.855	1.00	17.60
ATOM	782	O	SER	109	1.634	20.476	-8.994	1.00	17.60
ATOM	783	N	PHE	110	3.876	20.486	-8.827	1.00	17.60
ATOM	784	CA	PHE	110	4.055	21.889	-9.142	1.00	17.60
ATOM	785	CB	PHE	110	3.241	22.837	-8.287	1.00	17.60
ATOM	786	CG	PHE	110	3.348	22.860	-6.779	1.00	17.60
ATOM	787	CD1	PHE	110	2.493	22.060	-6.009	1.00	17.60
ATOM	788	CD2	PHE	110	4.181	23.712	-6.135	1.00	17.60
ATOM	789	CE1	PHE	110	2.435	22.149	-4.613	1.00	17.60
ATOM	790	CE2	PHE	110	4.116	23.792	-4.750	1.00	17.60
ATOM	791	CZ	PHE	110	3.253	23.029	-3.978	1.00	17.60
ATOM	792	C	PHE	110	5.488	22.211	-8.891	1.00	17.60
ATOM	793	O	PHE	110	6.172	21.324	-8.370	1.00	17.60
ATOM	794	N	LYS	111	5.974	23.420	-9.222	1.00	17.60
ATOM	795	CA	LYS	111	7.358	23.860	-8.922	1.00	17.60
TOM	796	CB	LYS	111	8.346	23.391	-10.037	1.00	17.60
:OM	797	CG	LYS	111	8.101	24.042	-11.419	1.00	17.60
ATOM	798	CD	LYS	111	8.761	23.448	-12.679	1.00	17.60
ATOM	799	CE	LYS	111	7.891	23.870	-13.882	1.00	17.60
ATOM	800	NZ	LYS	111	8.346	23.370	-15.168	1.00	17.60
ATOM	801	C	LYS	111	7.482	25.368	-8.767	1.00	17.60
ATOM	802	O	LYS	111	6.494	26.066	-9.092	1.00	17.60
ATOM	803	N	ASP	112	8.606	25.947	-8.254	1.00	17.60
ATOM	804	CA	ASP	112	8.781	27.399	-8.214	1.00	17.60
ATOM	805	CB	ASP	112	8.456	28.021	-6.866	1.00	17.60
ATOM	806	CG	ASP	112	9.276	27.751	-5.627	1.00	17.60
ATOM	807	OD1	ASP	112	10.493	27.820	-5.638	1.00	17.60
ATOM	808	OD2	ASP	112	8.664	27.516	-4.598	1.00	17.60
ATOM	809	C	ASP	112	10.189	27.757	-8.530	1.00	17.60
ATOM	810	O	ASP	112	10.984	26.898	-8.823	1.00	17.60
ATOM	811	N	ASN	113	10.677	28.959	-8.375	1.00	17.60
ATOM	812	CA	ASN	113	12.064	29.301	-8.778	1.00	17.60
ATOM	813	CB	ASN	113	12.270	30.768	-8.519	1.00	17.60
ATOM	814	CG	ASN	113	11.635	31.717	-9.547	1.00	17.60
ATOM	815	OD1	ASN	113	10.783	32.567	-9.262	1.00	17.60
ATOM	816	ND2	ASN	113	12.017	31.608	-10.804	1.00	17.60
ATOM	817	C	ASN	113	13.207	28.546	-8.199	1.00	17.60
ATOM	818	O	ASN	113	14.285	28.630	-8.762	1.00	17.60
ATOM	819	N	SER	114	12.987	27.793	-7.144	1.00	17.60
ATOM	820	CA	SER	114	14.033	27.026	-6.520	1.00	17.60
TOM	821	CB	SER	114	14.385	27.582	-5.142	1.00	17.60
:OM	822	OG	SER	114	14.648	28.964	-5.121	1.00	17.60
ATOM	823	C	SER	114	13.714	25.544	-6.335	1.00	17.60
ATOM	824	O	SER	114	14.652	24.734	-6.290	1.00	17.60
ATOM	825	N	ASN	115	12.445	25.105	-6.326	1.00	17.60
ATOM	826	CA	ASN	115	12.119	23.763	-5.907	1.00	17.60
ATOM	827	CB	ASN	115	11.601	23.749	-4.489	1.00	17.60
ATOM	828	CG	ASN	115	12.634	24.313	-3.558	1.00	17.60
ATOM	829	OD1	ASN	115	13.154	23.553	-2.725	1.00	17.60
ATOM	830	ND2	ASN	115	12.350	25.590	-2.995	1.00	17.60
ATOM	831	C	ASN	115	11.050	23.126	-6.749	1.00	17.60
ATOM	832	O	ASN	115	10.279	23.764	-7.449	1.00	17.60
ATOM	833	N	LEU	116	10.946	21.850	-6.481	1.00	17.60
ATOM	834	CA	LEU	116	10.060	20.927	-7.120	1.00	17.60
ATOX	835	CB	LEU	116	10.869	19.908	-7.884	1.00	17.60
ATOX	836	CG	LEU	116	11.936	20.415	-8.814	1.00	17.60
ATOX	837	CD1	LEU	116	12.929	19.325	-9.129	1.00	17.60
ATOX	838	CD2	LEU	116	11.228	21.018	-9.993	1.00	17.60
ATOX	839	C	LEU	116	9.306	20.221	-6.014	1.00	17.60
ATOX	840	O	LEU	116	9.879	19.588	-5.132	1.00	17.60
ATOX	841	N	TYR	117	8.001	20.243	-6.085	1.00	17.60
ATOX	842	CA	TYR	117	7.169	19.695	-5.041	1.00	17.60

ATOM	843	CB	TYR	117	6.304	20.817	-4.462	1.00	17.60
ATOM	844	CG	TYR	117	7.033	22.102	-4.125	1.00	17.60
ATOM	845	CD1	TYR	117	7.223	22.393	-2.802	1.00	17.60
ATOM	846	CE1	TYR	117	7.946	23.503	-2.440	1.00	17.60
ATOM	847	CD2	TYR	117	7.549	22.933	-5.106	1.00	17.60
ATOM	848	CE2	TYR	117	8.270	24.046	-4.758	1.00	17.60
ATOM	849	CZ	TYR	117	8.483	24.335	-3.409	1.00	17.60
ATOM	850	OH	TYR	117	9.284	25.417	-3.010	1.00	17.60
ATOM	851	C	TYR	117	6.281	18.602	-5.630	1.00	17.60
ATOM	852	O	TYR	117	5.877	18.601	-6.820	1.00	17.60
ATOM	853	N	MET	118	5.943	17.664	-4.771	1.00	17.60
ATOM	854	CA	MET	118	4.982	16.609	-5.121	1.00	17.60
ATOM	855	CB	MET	118	5.721	15.356	-5.428	1.00	17.60
ATOM	856	CG	MET	118	6.485	15.405	-6.683	1.00	17.60
ATOM	857	SD	MET	118	7.404	13.875	-6.665	1.00	17.60
ATOM	858	CE	MET	118	8.614	14.507	-7.767	1.00	17.60
ATOM	859	C	MET	118	4.069	16.398	-3.929	1.00	17.60
ATOM	860	O	MET	118	4.621	16.236	-2.862	1.00	17.60
ATOM	861	N	VAL	119	2.755	16.344	-3.930	1.00	17.60
ATOM	862	CA	VAL	119	2.041	16.318	-2.692	1.00	17.60
ATOM	863	CB	VAL	119	1.091	17.472	-2.662	1.00	17.60
ATOM	864	CG1	VAL	119	0.564	17.509	-1.263	1.00	17.60
ATOM	865	CG2	VAL	119	1.740	18.803	-2.975	1.00	17.60
ATOM	866	C	VAL	119	1.319	15.004	-2.667	1.00	17.60
ATOM	867	O	VAL	119	0.445	14.820	-3.486	1.00	17.60
ATOM	868	N	MET	120	1.616	14.075	-1.778	1.00	17.60
ATOM	869	CA	MET	120	1.057	12.730	-1.700	1.00	17.60
ATOM	870	CB	MET	120	2.087	11.658	-1.304	1.00	17.60
ATOM	871	CG	MET	120	2.961	10.918	-2.339	1.00	17.60
ATOM	872	SD	MET	120	4.298	11.751	-3.236	1.00	17.60
ATOM	873	CE	MET	120	5.646	11.781	-2.077	1.00	17.60
ATOM	874	C	MET	120	0.017	12.656	-0.627	1.00	17.60
ATOM	875	O	MET	120	0.024	13.537	0.210	1.00	17.60
ATOM	876	N	GLU	121	-0.836	11.663	-0.562	1.00	17.60
ATOM	877	CA	GLU	121	-1.762	11.401	0.547	1.00	17.60
ATOM	878	CB	GLU	121	-2.622	10.132	0.175	1.00	17.60
ATOM	879	CG	GLU	121	-4.029	9.811	0.752	1.00	17.60
ATOM	880	CD	GLU	121	-5.018	11.008	0.925	1.00	17.60
ATOM	881	OE1	GLU	121	-5.961	11.178	0.107	1.00	17.60
ATOM	882	OE2	GLU	121	-4.842	11.781	1.904	1.00	17.60
ATOM	883	C	GLU	121	-0.831	11.183	1.782	1.00	17.60
ATOM	884	O	GLU	121	0.339	10.775	1.615	1.00	17.60
ATOM	885	N	TYR	122	-1.229	11.496	3.036	1.00	17.60
ATOM	886	CA	TYR	122	-0.382	11.200	4.215	1.00	17.60
ATOM	887	CB	TYR	122	-0.547	12.358	5.297	1.00	17.60
ATOM	888	CG	TYR	122	-0.007	12.236	6.722	1.00	17.60
ATOM	889	CD1	TYR	122	1.336	12.114	7.020	1.00	17.60
ATOM	890	CE1	TYR	122	1.763	11.928	8.337	1.00	17.60
ATOM	891	CD2	TYR	122	-0.914	12.189	7.756	1.00	17.60
ATOM	892	CE2	TYR	122	-0.515	12.010	9.069	1.00	17.60
ATOM	893	CZ	TYR	122	0.873	11.881	9.354	1.00	17.60
ATOM	894	OH	TYR	122	1.395	11.740	10.677	1.00	17.60
ATOM	895	C	TYR	122	-0.782	9.825	4.773	1.00	17.60
ATOM	896	O	TYR	122	-1.952	9.490	5.034	1.00	17.60
ATOM	897	N	VAL	123	0.223	8.961	4.912	1.00	17.60
ATOM	898	CA	VAL	123	0.075	7.622	5.498	1.00	17.60
ATOM	899	CB	VAL	123	0.871	6.558	4.595	1.00	17.60
ATOM	900	CG1	VAL	123	0.558	5.138	5.048	1.00	17.60
ATOM	901	CG2	VAL	123	0.424	6.540	3.140	1.00	17.60
ATOM	902	C	VAL	123	0.668	7.786	6.928	1.00	17.60
ATOM	903	O	VAL	123	1.890	7.895	7.154	1.00	17.60
ATOM	904	N	ALA	124	-0.195	7.888	7.953	1.00	17.60
ATOM	905	CA	ALA	124	0.253	8.111	9.336	1.00	17.60
ATOM	906	CB	ALA	124	-0.856	8.633	10.323	1.00	17.60
ATOM	907	C	ALA	124	0.942	6.966	10.002	1.00	17.60

ATOM	908	O	ALA	124	1.619	7.188	11.015	1.00	17.60
ATOM	909	N	GLY	125	0.803	5.783	9.411	1.00	17.60
ATOM	910	CA	GLY	125	1.321	4.619	10.053	1.00	17.60
ATOM	911	C	GLY	125	2.781	4.748	10.287	1.00	17.60
ATOM	912	O	GLY	125	3.283	4.164	11.249	1.00	17.60
ATOM	913	N	GLY	126	3.468	5.557	9.491	1.00	17.60
ATOM	914	CA	GLY	126	4.895	5.672	9.620	1.00	17.60
ATOM	915	C	GLY	126	5.471	4.501	8.871	1.00	17.60
ATOM	916	O	GLY	126	4.799	3.589	8.397	1.00	17.60
ATOM	917	N	GLU	127	6.778	4.543	8.788	1.00	17.50
ATOM	918	CA	GLU	127	7.556	3.574	8.033	1.00	17.60
ATOM	919	CB	GLU	127	9.012	4.010	8.138	1.00	17.60
ATOM	920	CG	GLU	127	9.290	5.212	7.223	1.00	17.60
ATOM	921	CD	GLU	127	10.662	5.863	7.388	1.00	17.60
ATOM	922	OE1	GLU	127	11.631	5.105	7.442	1.00	17.60
ATOM	923	OE2	GLU	127	10.765	7.301	7.443	1.00	17.60
ATOM	924	C	GLU	127	7.371	2.126	8.480	1.00	17.60
ATOM	925	O	GLU	127	6.912	1.840	9.590	1.00	17.60
ATOM	926	N	MET	128	7.713	1.166	7.637	1.00	17.60
ATOM	927	CA	MET	128	7.707	-0.227	8.017	1.00	17.60
ATOM	928	CB	MET	128	7.739	-1.085	6.811	1.00	17.60
ATOM	929	CG	MET	128	7.206	-2.477	6.980	1.00	17.60
ATOM	930	SD	MET	128	8.115	-3.435	5.769	1.00	17.60
ATOM	931	CE	MET	128	9.353	-3.652	6.997	1.00	17.60
ATOM	932	C	MET	128	9.009	-0.384	8.758	1.00	17.60
ATOM	933	O	MET	128	9.141	-1.290	9.560	1.00	17.60
ATOM	934	N	PHE	129	10.012	0.450	8.478	1.00	17.60
ATOM	935	CA	PHE	129	11.313	0.501	9.117	1.00	17.60
ATOM	936	CB	PHE	129	12.147	1.571	8.430	1.00	17.60
ATOM	937	CG	PHE	129	13.521	1.780	9.005	1.00	17.60
ATOM	938	CD1	PHE	129	14.580	1.068	8.491	1.00	17.60
ATOM	939	CD2	PHE	129	13.725	2.642	10.021	1.00	17.60
ATOM	940	CE1	PHE	129	15.854	1.210	8.994	1.00	17.60
ATOM	941	CE2	PHE	129	14.996	2.768	10.511	1.00	17.60
ATOM	942	CZ	PHE	129	16.067	2.067	10.016	1.00	17.60
ATOM	943	C	PHE	129	11.246	0.786	10.592	1.00	17.60
ATOM	944	O	PHE	129	11.741	-0.040	11.339	1.00	17.60
ATOM	945	N	SER	130	10.709	1.918	11.024	1.00	17.60
ATOM	946	CA	SER	130	10.661	2.290	12.412	1.00	17.60
ATOM	947	CB	SER	130	9.782	3.527	12.527	1.00	17.60
ATOM	948	OG	SER	130	9.929	4.482	11.492	1.00	17.60
ATOM	949	C	SER	130	10.080	1.173	13.291	1.00	17.60
ATOM	950	O	SER	130	10.646	0.849	14.325	1.00	17.60
ATOM	951	N	HIS	131	9.014	0.494	12.917	1.00	17.60
ATOM	952	CA	HIS	131	8.457	-0.605	13.671	1.00	17.60
ATOM	953	CB	HIS	131	7.065	-0.868	13.271	1.00	17.60
ATOM	954	CG	HIS	131	6.277	0.414	13.213	1.00	17.60
ATOM	955	CD2	HIS	131	5.595	0.806	12.151	1.00	17.60
ATOM	956	ND1	HIS	131	6.211	1.369	14.145	1.00	17.60
ATOM	957	CE1	HIS	131	5.412	2.295	13.672	1.00	17.60
ATOM	958	NE2	HIS	131	4.997	1.969	12.477	1.00	17.60
ATOM	959	C	HIS	131	9.219	-1.894	13.447	1.00	17.60
ATOM	960	O	HIS	131	9.201	-2.756	14.292	1.00	17.60
ATOM	961	N	LEU	132	9.873	-2.149	12.335	1.00	17.60
ATOM	962	CA	LEU	132	10.695	-3.319	12.198	1.00	17.60
ATOM	963	CB	LEU	132	11.209	-3.405	10.776	1.00	17.60
ATOM	964	CG	LEU	132	12.351	-4.312	10.401	1.00	17.60
ATOM	965	CD1	LEU	132	11.860	-5.711	10.294	1.00	17.60
ATOM	966	CD2	LEU	132	12.963	-3.826	9.118	1.00	17.60
ATOM	967	C	LEU	132	11.834	-3.128	13.174	1.00	17.60
ATOM	968	O	LEU	132	12.096	-4.068	13.923	1.00	17.60
ATOM	969	N	ARG	133	12.563	-1.998	13.252	1.00	17.60
ATOM	970	CA	ARG	133	13.645	-1.852	14.200	1.00	17.60
ATOM	971	CB	ARG	133	14.381	-0.539	13.971	1.00	17.60
ATOM	972	CG	ARG	133	15.246	-0.337	12.722	1.00	17.60
ATOM	973	CD	ARG	133	16.509	-1.154	12.712	1.00	17.60
ATOM	974	NE	ARG	133	16.411	-2.149	11.665	1.00	17.60
ATOM	975	CZ	ARG	133	16.986	-1.999	10.468	1.00	17.60
ATOM	976	NH1	ARG	133	17.701	-0.934	10.129	1.00	17.60
ATOM	977	NH2	ARG	133	16.786	-2.931	9.566	1.00	17.60
ATOM	978	C	ARG	133	13.166	-1.892	15.641	1.00	17.60
ATOM	979	O	ARG	133	13.719	-2.656	16.405	1.00	17.60
ATOM	980	N	ARG	134	12.160	-1.127	16.059	1.00	17.60
ATOM	981	CA	ARG	134	11.617	-1.223	17.406	1.00	17.60
ATOM	982	CB	ARG	134	10.571	-0.173	17.527	1.00	17.60
ATOM	983	CG	ARG	134	9.494	-0.386	18.601	1.00	17.60
ATOM	984	CD	ARG	134	8.306	0.224	17.697	1.00	17.60
ATOM	985	NE	ARG	134	7.109	0.862	18.299	1.00	17.60
ATOM	986	CZ	ARG	134	5.833	0.517	17.943	1.00	17.60
ATOM	987	NH1	ARG	134	5.584	-0.425	16.990	1.00	17.60
ATOM	988	NH2	ARG	134	4.804	1.191	18.559	1.00	17.60
ATOM	989	C	ARG	134	11.043	-2.576	17.815	1.00	17.60
ATOM	990	O	ARG	134	11.221	-3.026	18.956	1.00	17.60
ATOM	991	N	ILE	135	10.280	-3.230	16.935	1.00	17.60
ATOM	992	CA	ILE	135	9.737	-4.549	17.230	1.00	17.60
ATOM	993	CB	ILE	135	8.598	-4.780	16.165	1.00	17.60
ATOM	994	CG2	ILE	135	8.175	-6.216	16.096	1.00	17.60
ATOM	995	CG1	ILE	135	7.405	-3.902	16.492	1.00	17.60
ATOM	996	CD1	ILE	135	6.259	-3.820	15.431	1.00	17.60
ATOM	997	C	ILE	135	10.879	-5.609	17.196	1.00	17.60
ATOM	998	O	ILE	135	10.820	-6.604	17.941	1.00	17.60
ATOM	999	N	GLY	136	11.928	-5.442	16.341	1.00	17.60
ATOM	1000	CA	GLY	136	13.076	-6.354	16.137	1.00	17.60
ATOM	1001	C	GLY	136	13.019	-7.406	14.993	1.00	17.60
ATOM	1002	O	GLY	136	13.990	-7.683	14.290	1.00	17.60
ATOM	1003	N	ARG	137	11.896	-8.031	14.766	1.00	17.60
ATOM	1004	CA	ARG	137	11.724	-9.123	13.839	1.00	17.60
ATOM	1005	CB	ARG	137	11.837	-10.485	14.474	1.00	17.60
ATOM	1006	CG	ARG	137	13.055	-11.348	14.677	1.00	17.60
ATOM	1007	CD	ARG	137	12.602	-12.629	15.406	1.00	17.60
ATOM	1008	NE	ARG	137	11.517	-13.344	14.691	1.00	17.60
ATOM	1009	CZ	ARG	137	11.090	-14.630	14.918	1.00	17.60
ATOM	1010	NH1	ARG	137	11.635	-15.398	15.878	1.00	17.60
ATOM	1011	NH2	ARG	137	10.194	-15.262	14.101	1.00	17.60
ATOM	1012	C	ARG	137	10.254	-9.037	13.424	1.00	17.60
ATOM	1013	O	ARG	137	9.444	-8.319	14.005	1.00	17.60
ATOM	1014	N	PHE	138	9.833	-9.752	12.412	1.00	17.60
ATOM	1015	CA	PHE	138	8.445	-9.905	12.128	1.00	17.60
ATOM	1016	CB	PHE	138	8.107	-9.239	10.777	1.00	17.60
ATOM	1017	CG	PHE	138	7.903	-7.736	10.926	1.00	17.60
ATOM	1018	CD1	PHE	138	8.339	-6.854	9.955	1.00	17.60
ATOM	1019	CD2	PHE	138	7.325	-7.186	12.059	1.00	17.60
ATOM	1020	CE1	PHE	138	8.204	-5.485	10.125	1.00	17.60
ATOM	1021	CE2	PHE	138	7.194	-5.816	12.225	1.00	17.60
ATOM	1022	CZ	PHE	138	7.634	-4.960	11.258	1.00	17.60
ATOM	1023	C	PHE	138	8.268	-11.432	12.128	1.00	17.60
ATOM	1024	O	PHE	138	9.146	-12.244	11.834	1.00	17.60
ATOM	1025	N	SEP	139	7.120	-11.854	12.667	1.00	17.60
ATOM	1026	CA	SEP	139	6.779	-13.266	12.651	1.00	17.60
ATOM	1027	CB	SEP	139	5.593	-13.527	13.505	1.00	17.60
ATOM	1028	OG	SEP	139	4.707	-12.396	13.489	1.00	17.60
ATOM	1029	PD	SEP	139	3.114	-12.809	13.805	1.00	17.80
ATOM	1030	OE1	SEP	139	2.286	-11.533	13.819	1.00	17.60
ATOM	1031	OE2	SEP	139	2.744	-13.900	12.825	1.00	17.60
ATOM	1032	OE3	SEP	139	3.351	-13.492	15.324	1.00	17.60
ATOM	1033	C	SEP	139	6.433	-13.567	11.232	1.00	17.60
ATOM	1034	O	SEP	139	5.822	-12.756	10.532	1.00	17.60
ATOM	1035	N	GLU	140	6.773	-14.802	10.923	1.00	17.60
ATOM	1036	CA	GLU	140	6.700	-15.280	9.565	1.00	17.60
ATOM	1037	CB	GLU	140	7.060	-16.779	9.650	1.00	17.60

ATOM	1038	CG	GLU	140	7.591	-17.418	8.354	1.00	17.60
ATOM	1039	CD	GLU	140	8.821	-18.290	8.558	1.00	17.60
ATOM	1040	OE1	GLU	140	8.745	-19.493	8.344	1.00	17.60
ATOM	1041	OE2	GLU	140	9.866	-17.767	8.919	1.00	17.60
ATOM	1042	C	GLU	140	5.367	-14.979	8.868	1.00	17.60
ATOM	1043	O	GLU	140	5.391	-14.429	7.765	1.00	17.60
ATOM	1044	N	PRO	141	4.196	-15.170	9.485	1.00	17.60
ATOM	1045	CD	PRO	141	3.994	-15.981	10.676	1.00	17.60
ATOM	1046	CA	PRO	141	2.893	-14.737	8.978	1.00	17.60
ATOM	1047	CB	PRO	141	1.918	-15.241	9.996	1.00	17.60
ATOM	1048	CG	PRO	141	2.601	-16.490	10.476	1.00	17.60
ATOM	1049	C	PRO	141	2.715	-13.263	8.749	1.00	17.60
ATOM	1050	O	PRO	141	1.998	-12.776	7.885	1.00	17.60
ATOM	1051	N	HIS	142	3.342	-12.572	9.659	1.00	17.60
ATOM	1052	CA	HIS	142	3.305	-11.166	9.556	1.00	17.60
ATOM	1053	CB	HIS	142	3.719	-10.581	10.911	1.00	17.60
ATOM	1054	CG	HIS	142	3.438	-9.081	11.117	1.00	17.60
ATOM	1055	CD2	HIS	142	2.872	-8.232	10.194	1.00	17.60
ATOM	1056	ND1	HIS	142	3.782	-8.312	12.172	1.00	17.60
ATOM	1057	CE1	HIS	142	3.474	-7.067	11.917	1.00	17.60
ATOM	1058	NE2	HIS	142	2.927	-7.032	10.728	1.00	17.60
ATOM	1059	C	HIS	142	4.272	-10.860	8.384	1.00	17.60
ATOM	1060	O	HIS	142	3.875	-10.053	7.526	1.00	17.60
ATOM	1061	N	ALA	143	5.445	-11.483	8.209	1.00	17.60
ATOM	1062	CA	ALA	143	6.363	-11.106	7.153	1.00	17.60
ATOM	1063	CB	ALA	143	7.597	-11.926	7.253	1.00	17.60
ATOM	1064	C	ALA	143	5.603	-11.411	5.857	1.00	17.60
ATOM	1065	O	ALA	143	5.545	-10.577	4.955	1.00	17.60
ATOM	1066	N	ARG	144	4.876	-12.507	5.737	1.00	17.60
ATOM	1067	CA	ARG	144	4.101	-12.836	4.548	1.00	17.60
ATOM	1068	CB	ARG	144	3.432	-14.131	4.749	1.00	17.60
ATOM	1069	CG	ARG	144	2.858	-14.890	3.614	1.00	17.60
ATOM	1070	CD	ARG	144	2.284	-16.163	4.247	1.00	17.60
ATOM	1071	NE	ARG	144	3.320	-17.120	4.581	1.00	17.60
ATOM	1072	CZ	ARG	144	3.352	-17.817	5.710	1.00	17.60
ATOM	1073	NH1	ARG	144	2.368	-17.614	6.573	1.00	17.60
ATOM	1074	NH2	ARG	144	4.387	-18.677	5.963	1.00	17.60
ATOM	1075	C	ARG	144	3.046	-11.815	4.275	1.00	17.60
ATOM	1076	O	ARG	144	2.812	-11.616	3.099	1.00	17.60
ATOM	1077	N	PHE	145	2.390	-11.159	5.229	1.00	17.60
ATOM	1078	CA	PHE	145	1.401	-10.133	4.916	1.00	17.60
ATOM	1079	CB	PHE	145	0.836	-9.582	6.257	1.00	17.60
ATOM	1080	CG	PHE	145	-0.364	-8.612	6.121	1.00	17.60
ATOM	1081	CD1	PHE	145	-1.587	-9.066	5.762	1.00	17.60
ATOM	1082	CD2	PHE	145	-0.172	-7.266	6.366	1.00	17.60
ATOM	1083	CE1	PHE	145	-2.647	-8.213	5.625	1.00	17.60
ATOM	1084	CE2	PHE	145	-1.243	-6.400	6.203	1.00	17.60
ATOM	1085	CZ	PHE	145	-2.479	-6.883	5.842	1.00	17.60
ATOM	1086	C	PHE	145	2.015	-8.994	4.036	1.00	17.60
ATOM	1087	O	PHE	145	1.497	-8.622	2.959	1.00	17.60
ATOM	1088	N	TYR	146	3.160	-8.404	4.378	1.00	17.60
ATOM	1089	CA	TYR	146	3.724	-7.359	3.570	1.00	17.60
ATOM	1090	CB	TYR	146	4.808	-6.693	4.356	1.00	17.60
ATOM	1091	CG	TYR	146	4.292	-6.183	5.674	1.00	17.60
ATOM	1092	CD1	TYR	146	3.108	-5.496	5.676	1.00	17.60
ATOM	1093	CE1	TYR	146	2.580	-5.030	6.859	1.00	17.60
ATOM	1094	CD2	TYR	146	4.963	-6.409	6.857	1.00	17.60
ATOM	1095	CE2	TYR	146	4.477	-5.930	8.053	1.00	17.60
ATOM	1096	CZ	TYR	146	3.228	-5.246	8.039	1.00	17.60
ATOM	1097	OH	TYR	146	2.610	-4.814	9.181	1.00	17.60
ATOM	1098	C	TYR	146	4.277	-7.992	2.315	1.00	17.60
ATOM	1099	O	TYR	146	4.148	-7.406	1.270	1.00	17.60
ATOM	1100	N	ALA	147	4.861	-9.185	2.361	1.00	17.60
ATOM	1101	CA	ALA	147	5.466	-9.828	1.198	1.00	17.60
ATOM	1102	CB	ALA	147	6.163	-11.106	1.627	1.00	17.60
ATOM	1103	C	ALA	147	4.388	-10.154	0.157	1.00	17.60
ATOM	1104	O	ALA	147	4.644	-10.075	-1.057	1.00	17.60
ATOM	1105	N	ALA	148	3.353	-10.450	0.565	1.00	17.60
ATOM	1106	CA	ALA	148	2.353	-10.681	-0.442	1.00	17.60
ATOM	1107	CB	ALA	148	0.928	-11.192	0.200	1.00	17.60
ATOM	1108	C	ALA	148	1.909	-9.329	-1.065	1.00	17.60
ATOM	1109	O	ALA	148	2.150	-9.209	-2.233	1.00	17.60
ATOM	1110	N	GLN	149	1.521	-8.272	-0.373	1.00	17.60
ATOM	1111	CA	GLN	149	1.415	-6.956	-1.000	1.00	17.60
ATOM	1112	CB	GLN	149	1.273	-5.839	0.004	1.00	17.60
ATOM	1113	CG	GLN	149	-0.091	-5.899	0.619	1.00	17.60
ATOM	1114	CD	GLN	149	-0.083	-5.216	1.942	1.00	17.60
ATOM	1115	OE1	GLN	149	-0.456	-4.058	2.027	1.00	17.60
ATOM	1116	NE2	GLN	149	0.347	-5.880	3.007	1.00	17.60
ATOM	1117	C	GLN	149	2.564	-6.493	-1.879	1.00	17.60
ATOM	1118	O	GLN	149	2.263	-5.808	-2.846	1.00	17.60
ATOM	1119	N	ILE	150	3.859	-6.760	-1.643	1.00	17.60
ATOM	1120	CA	ILE	150	4.906	-6.319	-2.549	1.00	17.60
ATOM	1121	CB	ILE	150	6.316	-6.350	-1.905	1.00	17.60
ATOM	1122	CG2	ILE	150	7.347	-6.157	-2.968	1.00	17.60
ATOM	1123	CG1	ILE	150	6.504	-5.239	-0.811	1.00	17.60
ATOM	1124	CD1	ILE	150	6.139	-3.784	-1.024	1.00	17.60
ATOM	1125	C	ILE	150	4.849	-7.261	-3.729	1.00	17.60
ATOM	1126	O	ILE	150	5.022	-6.744	-4.825	1.00	17.60
ATOM	1127	N	VAL	151	4.531	-8.571	-3.650	1.00	17.60
ATOM	1128	CA	VAL	151	4.425	-9.416	-4.841	1.00	17.60
ATOM	1129	CB	VAL	151	3.990	-10.843	-4.412	1.00	17.60
ATOM	1130	CG1	VAL	151	3.460	-11.635	-5.593	1.00	17.60
ATOM	1131	CG2	VAL	151	5.193	-11.520	-3.757	1.00	17.60
ATOM	1132	C	VAL	151	3.432	-8.746	-5.800	1.00	17.60
ATOM	1133	O	VAL	151	3.867	-8.303	-6.862	1.00	17.60
ATOM	1134	N	LEU	152	2.196	-8.444	-5.418	1.00	17.60
ATOM	1135	CA	LEU	152	1.209	-7.850	-6.323	1.00	17.60
ATOM	1136	CB	LEU	152	-0.145	-7.806	-5.618	1.00	17.60
ATOM	1137	CG	LEU	152	-0.827	-8.949	-6.852	1.00	17.60
ATOM	1138	CD1	LEU	152	-2.313	-8.609	-4.723	1.00	17.60
ATOM	1139	CD2	LEU	152	-0.846	-10.264	-5.646	1.00	17.60
ATOM	1140	C	LEU	152	1.520	-6.419	-6.854	1.00	17.60
ATOM	1141	O	LEU	152	1.196	-6.030	-8.003	1.00	17.60
ATOM	1142	N	THR	153	2.114	-5.592	-5.961	1.00	17.60
ATOM	1143	CA	THR	153	2.564	-4.265	-6.311	1.00	17.60
ATOM	1144	CB	THR	153	3.125	-3.566	-5.106	1.00	17.60
ATOM	1145	OG1	THR	153	2.112	-3.574	-4.148	1.00	17.60
ATOM	1146	OG2	THR	153	3.451	-2.138	-5.329	1.00	17.60
ATOM	1147	C	THR	153	3.592	-4.438	-7.368	1.00	17.60
ATOM	1148	O	THR	153	3.516	-3.795	-8.412	1.00	17.60
ATOM	1149	N	PHE	154	4.501	-5.369	-7.178	1.00	17.60
ATOM	1150	CA	PHE	154	5.548	-5.491	-8.114	1.00	17.60
ATOM	1151	CB	PHE	154	6.597	-6.378	-7.565	1.00	17.60
ATOM	1152	CG	PHE	154	7.733	-5.598	-6.912	1.00	17.60
ATOM	1153	CD1	PHE	154	7.665	-4.229	-6.771	1.00	17.60
ATOM	1154	CD2	PHE	154	8.828	-6.310	-6.450	1.00	17.60
ATOM	1155	CE1	PHE	154	8.715	-3.603	-6.161	1.00	17.60
ATOM	1156	CE2	PHE	154	9.874	-5.678	-5.838	1.00	17.60
ATOM	1157	CZ	PHE	154	9.805	-4.321	-5.700	1.00	17.60
ATOM	1158	C	PHE	154	5.057	-6.013	-9.473	1.00	17.60
ATOM	1159	O	PHE	154	5.536	-5.524	-10.440	1.00	17.60
ATOM	1160	N	GLU	155	4.113	-6.930	-9.429	1.00	17.60
ATOM	1161	CA	GLU	155	3.487	-7.456	-10.625	1.00	17.60
ATOM	1162	CB	GLU	155	2.494	-8.510	-10.233	1.00	17.60
ATOM	1163	CG	GLU	155	1.847	-9.328	-11.350	1.00	17.60
ATOM	1164	CD	GLU	155	0.777	-10.240	-10.903	1.00	17.60
ATOM	1165	OE1	GLU	155	0.839	-11.498	-11.347	1.00	17.60
ATOM	1166	OE2	GLU	155	-0.131	-9.961	-10.139	1.00	17.60
ATOM	1167	C	GLU	155	2.771	-6.401	-11.436	1.00	17.60

ATOM	1168	O	GLU	155	2.807	-6.420	-12.662	1.00	17.60
ATOM	1169	N	TYR	156	2.062	-5.494	-10.823	1.00	17.60
ATOM	1170	CA	TYR	156	1.463	-4.435	-11.570	1.00	17.60
ATOM	1171	CB	TYR	156	0.561	-3.767	-10.654	1.00	17.60
ATOM	1172	CG	TYR	156	0.215	-2.367	-10.974	1.00	17.60
ATOM	1173	CD1	TYR	156	-0.719	-2.079	-11.965	1.00	17.60
ATOM	1174	CE1	TYR	156	-1.057	-0.783	-12.210	1.00	17.60
ATOM	1175	CD2	TYR	156	0.828	-1.364	-10.228	1.00	17.60
ATOM	1176	CE2	TYR	156	0.485	-0.062	-10.480	1.00	17.60
ATOM	1177	CZ	TYR	156	-0.450	0.201	-11.463	1.00	17.60
ATOM	1178	OH	TYR	156	-0.811	1.513	-11.685	1.00	17.60
ATOM	1179	C	TYR	156	2.544	-3.525	-12.074	1.00	17.60
ATOM	1180	O	TYR	156	2.595	-3.178	-13.236	1.00	17.60
ATOM	1181	N	LEU	157	3.431	-3.138	-11.195	1.00	17.60
ATOM	1182	CA	LEU	157	4.531	-2.289	-11.581	1.00	17.60
ATOM	1183	CB	LEU	157	5.432	-2.099	-10.411	1.00	17.60
ATOM	1184	CG	LEU	157	5.832	-0.700	-10.023	1.00	17.60
ATOM	1185	CD1	LEU	157	4.709	0.293	-10.069	1.00	17.60
ATOM	1186	CD2	LEU	157	6.288	-0.791	-8.605	1.00	17.60
ATOM	1187	C	LEU	157	5.349	-2.821	-12.736	1.00	17.60
ATOM	1188	O	LEU	157	5.891	-2.081	-13.540	1.00	17.60
ATOM	1189	N	HIS	158	5.514	-4.109	-12.905	1.00	17.60
ATOM	1190	CA	HIS	158	6.259	-4.639	-14.028	1.00	17.60
ATOM	1191	CB	HIS	158	6.850	-5.970	-13.665	1.00	17.60
ATOM	1192	CG	HIS	158	7.856	-5.734	-12.582	1.00	17.60
ATOM	1193	CD2	HIS	158	8.360	-6.698	-11.767	1.00	17.60
ATOM	1194	ND1	HIS	158	8.395	-4.570	-12.252	1.00	17.60
ATOM	1195	CE1	HIS	158	9.209	-4.812	-11.260	1.00	17.60
ATOM	1196	NE2	HIS	158	9.188	-6.086	-10.974	1.00	17.60
ATOM	1197	C	HIS	158	5.452	-4.801	-15.296	1.00	17.60
ATOM	1198	O	HIS	158	6.067	-4.713	-16.375	1.00	17.60
ATOM	1199	N	SER	159	4.112	-5.008	-15.190	1.00	17.60
ATOM	1200	CA	SER	159	3.258	-5.174	-16.373	1.00	17.60
ATOM	1201	CB	SER	159	1.858	-5.491	-16.005	1.00	17.60
ATOM	1202	OG	SER	159	1.435	-4.464	-15.164	1.00	17.60
ATOM	1203	C	SER	159	3.216	-3.089	-17.170	1.00	17.60
ATOM	1204	O	SER	159	3.027	-3.912	-18.385	1.00	17.60
ATOM	1205	N	LEU	160	3.344	-2.776	-16.449	1.00	17.60
ATOM	1206	CA	LEU	160	3.573	-1.504	-17.076	1.00	17.60
ATOM	1207	CB	LEU	160	3.174	-0.523	-16.107	1.00	17.60
ATOM	1208	CG	LEU	160	1.831	0.012	-16.139	1.00	17.60
ATOM	1209	CD1	LEU	160	0.754	-0.946	-16.568	1.00	17.60
ATOM	1210	CD2	LEU	160	1.744	0.594	-14.750	1.00	17.60
ATOM	1211	C	LEU	160	5.020	-1.241	-17.538	1.00	17.60
ATOM	1212	O	LEU	160	5.369	-0.109	-17.869	1.00	17.60
ATOM	1213	N	ASP	161	5.885	-2.264	-17.587	1.00	17.60
ATOM	1214	CA	ASP	161	7.321	-2.184	-17.861	1.00	17.60
ATOM	1215	CB	ASP	161	7.514	-1.919	-19.329	1.00	17.60
ATOM	1216	CG	ASP	161	7.428	-3.242	-20.132	1.00	17.60
ATOM	1217	OD1	ASP	161	6.434	-3.353	-20.880	1.00	17.60
ATOM	1218	OD2	ASP	161	8.338	-4.134	-19.996	1.00	17.60
ATOM	1219	C	ASP	161	8.223	-1.257	-17.020	1.00	17.60
ATOM	1220	O	ASP	161	9.382	-0.957	-17.358	1.00	17.60
ATOM	1221	N	LEU	162	7.677	-0.932	-15.837	1.00	17.60
ATOM	1222	CA	LEU	162	8.346	-0.133	-14.865	1.00	17.60
ATOM	1223	CB	LEU	162	7.376	0.501	-13.897	1.00	17.60
ATOM	1224	CG	LEU	162	6.557	1.762	-14.141	1.00	17.60
ATOM	1225	CD1	LEU	162	6.716	2.251	-15.513	1.00	17.60
ATOM	1226	CD2	LEU	162	5.100	1.486	-13.941	1.00	17.60
ATOM	1227	C	LEU	162	9.180	-1.161	-14.146	1.00	17.60
ATOM	1228	O	LEU	162	8.928	-2.378	-14.071	1.00	17.60
ATOM	1229	N	ILE	163	10.254	-0.594	-13.639	1.00	17.60
ATOM	1230	CA	ILE	163	11.202	-1.228	-12.758	1.00	17.60
ATOM	1231	CB	ILE	163	12.460	-1.694	-13.650	1.00	17.60
ATOM	1232	CG2	ILE	163	12.870	-0.565	-14.669	1.00	17.60
ATOM	1233	CG1	ILE	163	13.561	-1.899	-12.721	1.00	17.60
ATOM	1234	CD1	ILE	163	14.833	-2.255	-13.467	1.00	17.60
ATOM	1235	C	ILE	163	11.328	-0.105	-11.702	1.00	17.60
ATOM	1236	O	ILE	163	11.350	1.064	-12.048	1.00	17.60
ATOM	1237	N	TYR	164	11.224	-0.445	-10.399	1.00	17.60
ATOM	1238	CA	TYR	164	11.163	0.421	-9.180	1.00	17.60
ATOM	1239	CB	TYR	164	9.987	-0.015	-8.232	1.00	17.60
ATOM	1240	CG	TYR	164	9.937	0.522	-6.817	1.00	17.60
ATOM	1241	CD1	TYR	164	9.272	1.687	-6.534	1.00	17.60
ATOM	1242	CE1	TYR	164	9.347	2.255	-5.289	1.00	17.60
ATOM	1243	CD2	TYR	164	10.653	-0.091	-5.832	1.00	17.60
ATOM	1244	CE2	TYR	164	10.750	0.462	-4.581	1.00	17.60
ATOM	1245	CZ	TYR	164	10.105	1.631	-4.342	1.00	17.60
ATOM	1246	OH	TYR	164	10.352	2.242	-3.158	1.00	17.60
ATOM	1247	C	TYR	164	12.457	0.044	-8.557	1.00	17.60
ATOM	1248	O	TYR	164	12.530	-1.113	-8.143	1.00	17.60
ATOM	1249	N	ARG	165	13.483	0.835	-8.436	1.00	17.60
ATOM	1250	CA	ARG	165	14.671	0.185	-7.923	1.00	17.60
ATOM	1251	CB	ARG	165	15.786	0.513	-8.865	1.00	17.60
ATOM	1252	CG	ARG	165	15.477	-0.051	-10.228	1.00	17.60
ATOM	1253	CD	ARG	165	16.388	0.546	-11.257	1.00	17.60
ATOM	1254	NE	ARG	165	16.032	1.915	-11.467	1.00	17.60
ATOM	1255	CZ	ARG	165	16.671	2.608	-12.376	1.00	17.60
ATOM	1256	NH1	ARG	165	17.636	2.027	-13.074	1.00	17.60
ATOM	1257	NH2	ARG	165	16.337	3.875	-12.593	1.00	17.60
ATOM	1258	C	ARG	165	15.056	0.509	-6.508	1.00	17.60
ATOM	1259	O	ARG	165	16.246	0.679	-6.261	1.00	17.60
ATOM	1260	N	ASP	166	14.175	0.593	-5.520	1.00	17.60
ATOM	1261	CA	ASP	166	14.587	1.059	-4.206	1.00	17.60
ATOM	1262	CB	ASP	166	14.533	2.586	-4.317	1.00	17.60
ATOM	1263	CG	ASP	166	15.325	3.457	-3.337	1.00	17.60
ATOM	1264	OD1	ASP	166	16.174	2.923	-2.596	1.00	17.60
ATOM	1265	OD2	ASP	166	15.087	4.681	-3.357	1.00	17.60
ATOM	1266	C	ASP	166	13.749	0.498	-3.051	1.00	17.60
ATOM	1267	O	ASP	166	13.250	1.172	-2.150	1.00	17.60
ATOM	1268	N	LEU	167	13.514	-0.791	-3.054	1.00	17.60
ATOM	1269	CA	LEU	167	12.693	-1.403	-2.026	1.00	17.60
ATOM	1270	CB	LEU	167	12.216	-2.786	-2.483	1.00	17.60
ATOM	1271	CG	LEU	167	11.150	-3.467	-1.691	1.00	17.60
ATOM	1272	CD1	LEU	167	9.846	-2.771	-1.918	1.00	17.60
ATOM	1273	CD2	LEU	167	11.098	-4.926	-2.105	1.00	17.60
ATOM	1274	C	LEU	167	13.629	-1.516	-0.837	1.00	17.60
ATOM	1275	O	LEU	167	14.804	-1.887	-0.961	1.00	17.60
ATOM	1276	N	LYS	168	13.144	-1.028	0.283	1.00	17.60
ATOM	1277	CA	LYS	168	13.820	-1.146	1.538	1.00	17.60
ATOM	1278	CB	LYS	168	14.934	-0.130	1.663	1.00	17.60
ATOM	1279	CG	LYS	168	14.556	1.257	1.357	1.00	17.60
ATOM	1280	CD	LYS	168	15.812	2.011	1.457	1.00	17.60
ATOM	1281	CE	LYS	168	15.415	3.339	0.864	1.00	17.60
ATOM	1282	NZ	LYS	168	16.489	4.325	0.841	1.00	17.60
ATOM	1283	C	LYS	168	12.704	-0.836	2.487	1.00	17.60
ATOM	1284	O	LYS	168	11.789	-0.141	2.089	1.00	17.60
ATOM	1285	N	PRO	169	12.718	-1.316	3.724	1.00	17.60
ATOM	1286	CD	PRO	169	13.423	-2.526	4.094	1.00	17.60
ATOM	1287	CA	PRO	169	11.950	-0.839	4.862	1.00	17.60
ATOM	1288	CB	PRO	169	12.809	-1.287	5.970	1.00	17.60
ATOM	1289	CG	PRO	169	13.033	-2.677	5.523	1.00	17.60
ATOM	1290	C	PRO	169	11.503	0.606	4.989	1.00	17.60
ATOM	1291	O	PRO	169	10.363	0.938	5.337	1.00	17.60
ATOM	1292	N	GLU	170	12.467	1.466	4.716	1.00	17.60
ATOM	1293	CA	GLU	170	12.322	2.901	4.791	1.00	17.60
ATOM	1294	CB	GLU	170	13.635	3.580	4.406	1.00	17.60
ATOM	1295	CG	GLU	170	14.871	3.236	5.296	1.00	17.60
ATOM	1296	CD	GLU	170	15.660	1.961	5.080	1.00	17.60
ATOM	1297	OE1	GLU	170	15.103	0.875	4.938	1.00	17.60

ATOM	1298	OE2	GLU	170	16.971	1.952	5.052	1.00	17.60
ATOM	1299	C	GLU	170	11.235	3.161	3.791	1.00	17.60
ATOM	1300	O	GLU	170	10.130	3.518	4.234	1.00	17.60
ATOM	1301	N	ASN	171	11.320	2.788	2.512	1.00	17.60
ATOM	1302	CA	ASN	171	10.286	3.022	1.499	1.00	17.60
ATOM	1303	CB	ASN	171	10.843	2.585	0.192	1.00	17.60
ATOM	1304	CG	ASN	171	11.742	3.632	-0.370	1.00	17.60
ATOM	1305	OD1	ASN	171	12.265	4.468	0.357	1.00	17.60
ATOM	1306	ND2	ASN	171	12.026	3.596	-1.646	1.00	17.60
ATOM	1307	C	ASN	171	8.879	2.436	1.628	1.00	17.60
ATOM	1308	O	ASN	171	8.066	2.585	0.708	1.00	17.60
ATOM	1309	N	LEU	172	8.675	1.826	2.740	1.00	17.60
ATOM	1310	CA	LEU	172	7.369	1.223	2.798	1.00	17.60
ATOM	1311	CB	LEU	172	7.342	-0.282	2.998	1.00	17.60
ATOM	1312	CG	LEU	172	8.137	-1.105	2.061	1.00	17.60
ATOM	1313	CD1	LEU	172	8.440	-2.487	2.555	1.00	17.60
ATOM	1314	CD2	LEU	172	7.342	-1.141	0.851	1.00	17.60
ATOM	1315	C	LEU	172	6.475	1.879	3.980	1.00	17.60
ATOM	1316	O	LEU	172	7.055	1.795	5.054	1.00	17.60
ATOM	1317	N	LEU	173	5.312	2.530	3.862	1.00	17.60
ATOM	1318	CA	LEU	173	4.621	3.203	4.911	1.00	17.60
ATOM	1319	CB	LEU	173	4.125	4.557	4.496	1.00	17.60
ATOM	1320	CG	LEU	173	5.064	5.707	4.199	1.00	17.60
ATOM	1321	CD1	LEU	173	4.317	7.005	4.153	1.00	17.60
ATOM	1322	CD2	LEU	173	6.074	5.823	5.316	1.00	17.60
ATOM	1323	C	LEU	173	3.421	2.412	5.337	1.00	17.60
ATOM	1324	O	LEU	173	2.822	1.806	4.443	1.00	17.60
ATOM	1325	N	ILE	174	3.010	2.393	6.625	1.00	17.60
ATOM	1326	CA	ILE	174	1.925	1.526	7.114	1.00	17.60
ATOM	1327	CB	ILE	174	2.240	1.013	8.504	1.00	17.60
ATOM	1328	CG2	ILE	174	1.087	0.161	8.966	1.00	17.60
ATOM	1329	CG1	ILE	174	3.589	0.266	8.532	1.00	17.60
ATOM	1330	CD1	ILE	174	3.832	-0.952	7.620	1.00	17.60
ATOM	1331	C	ILE	174	0.687	2.340	7.179	1.00	17.60
ATOM	1332	O	ILE	174	0.802	3.453	7.668	1.00	17.60
ATOM	1333	N	ASP	175	-0.466	1.893	6.714	1.00	17.60
ATOM	1334	CA	ASP	175	-1.617	2.758	6.819	1.00	17.60
ATOM	1335	CB	ASP	175	-2.360	2.717	5.560	1.00	17.60
ATOM	1336	CG	ASP	175	-2.020	1.380	5.195	1.00	17.60
ATOM	1337	OD1	ASP	175	-2.679	1.100	4.034	1.00	17.60
ATOM	1338	OD2	ASP	175	-3.315	0.648	5.999	1.00	17.60
ATOM	1339	C	ASP	175	-2.594	2.551	7.939	1.00	17.60
ATOM	1340	O	ASP	175	-2.246	1.740	8.772	1.00	17.60
ATOM	1341	N	GLN	176	-3.845	3.062	7.983	1.00	17.60
TOM	1342	CA	GLN	176	-4.774	2.924	9.098	1.00	17.60
.TOM	1343	CB	GLN	176	-5.698	4.137	9.197	1.00	17.60
ATOM	1344	CG	GLN	176	-6.594	4.105	10.456	1.00	17.60
ATOM	1345	CD	GLN	176	-7.023	5.030	10.567	1.00	17.60
ATOM	1346	OE1	GLN	176	-7.785	5.989	11.347	1.00	17.60
ATOM	1347	NE2	GLN	176	-8.960	4.788	9.885	1.00	17.60
ATOM	1348	C	GLN	176	-5.589	1.690	8.896	1.00	17.60
ATOM	1349	O	GLN	176	-6.818	1.669	8.869	1.00	17.60
ATOM	1350	N	GLN	177	-4.846	0.626	8.708	1.00	17.60
ATOM	1351	CA	GLN	177	-5.374	-0.709	8.452	1.00	17.60
ATOM	1352	CB	GLN	177	-6.184	-0.823	7.082	1.00	17.60
ATOM	1353	CG	GLN	177	-7.706	-0.598	6.921	1.00	17.60
ATOM	1354	CD	GLN	177	-8.531	-1.750	6.256	1.00	17.60
ATOM	1355	OE1	GLN	177	-9.253	-1.506	5.275	1.00	17.60
ATOM	1356	NE2	GLN	177	-8.566	-3.037	6.705	1.00	17.60
ATOM	1357	C	GLN	177	-4.145	-1.651	8.383	1.00	17.60
ATOM	1358	O	GLN	177	-4.334	-2.809	8.001	1.00	17.60
ATOM	1359	N	GLY	178	-2.891	-1.229	8.688	1.00	17.60
ATOM	1360	CA	GLY	178	-1.720	-2.121	8.692	1.00	17.60
ATOM	1361	C	GLY	178	-1.259	-2.752	7.366	1.00	17.60
ATOM	1362	O	GLY	178	-0.575	-3.799	7.418	1.00	17.60
ATOM	1363	N	TYR	179	-1.598	-2.086	6.229	1.00	17.60
ATOM	1364	CA	TYR	179	-1.276	-2.498	4.866	1.00	17.60
ATOM	1365	CB	TYR	179	-2.423	-2.392	3.914	1.00	17.60
ATOM	1366	CG	TYR	179	-3.666	-3.507	3.962	1.00	17.60
ATOM	1367	CD1	TYR	179	-3.534	-4.387	2.893	1.00	17.60
ATOM	1368	CE1	TYR	179	-4.672	-5.397	2.843	1.00	17.60
ATOM	1369	CD2	TYR	179	-4.366	-3.668	5.007	1.00	17.60
ATOM	1370	CE2	TYR	179	-5.315	-4.656	4.966	1.00	17.60
ATOM	1371	CZ	TYR	179	-5.352	-5.510	3.884	1.00	17.60
ATOM	1372	OH	TYR	179	-6.287	-6.526	3.807	1.00	17.60
ATOM	1373	C	TYR	179	-0.259	-1.523	4.377	1.00	17.60
ATOM	1374	O	TYR	179	-0.225	-0.368	4.856	1.00	17.60
ATOM	1375	N	ILE	180	0.615	-1.928	3.447	1.00	17.60
ATOM	1376	CA	ILE	180	1.719	-1.038	3.116	1.00	17.60
ATOM	1377	CB	ILE	180	3.079	-1.833	2.789	1.00	17.60
ATOM	1378	CG2	ILE	180	3.542	-2.504	4.032	1.00	17.60
ATOM	1379	CG1	ILE	180	2.964	-2.837	1.754	1.00	17.60
ATOM	1380	CD1	ILE	180	3.233	-2.287	0.332	1.00	17.60
ATOM	1381	C	ILE	180	1.328	-0.153	1.951	1.00	17.60
ATOM	1382	O	ILE	180	0.299	-0.366	1.310	1.00	17.60
ATOM	1383	N	GLN	181	2.330	0.920	1.821	1.00	17.60
ATOM	1384	CA	GLN	181	2.105	1.933	0.788	1.00	17.60
ATOM	1385	CB	GLN	181	1.315	3.078	1.219	1.00	17.60
ATOM	1386	CG	GLN	181	-0.092	2.598	1.296	1.00	17.60
ATOM	1387	CD	GLN	181	-1.036	3.533	0.621	1.00	17.60
ATOM	1388	OE1	GLN	181	-0.871	4.749	0.672	1.00	17.60
ATOM	1389	NE2	GLN	181	-2.070	3.051	-0.039	1.00	17.60
ATOM	1390	C	GLN	181	3.514	2.414	0.471	1.00	17.60
ATOM	1391	O	GLN	181	4.204	3.029	1.273	1.00	17.60
ATOM	1392	N	VAL	182	3.925	1.970	-0.738	1.00	17.60
ATOM	1393	CA	VAL	182	5.164	2.312	-1.407	1.00	17.60
ATOM	1394	CB	VAL	182	5.383	1.435	-2.594	1.00	17.60
ATOM	1395	CG1	VAL	182	6.841	1.481	-2.801	1.00	17.60
ATOM	1396	CG2	VAL	182	4.983	0.018	-2.615	1.00	17.60
ATOM	1397	C	VAL	182	5.111	3.768	-1.868	1.00	17.60
ATOM	1398	O	VAL	182	4.327	4.292	-2.654	1.00	17.60
ATOM	1399	N	THR	183	5.978	4.464	-1.196	1.00	17.60
ATOM	1400	CA	THR	183	6.230	5.878	-1.350	1.00	17.60
ATOM	1401	CB	THR	183	6.387	6.401	0.101	1.00	17.60
ATOM	1402	OG1	THR	183	6.318	7.834	0.076	1.00	17.60
ATOM	1403	CG2	THR	183	7.663	5.870	0.743	1.00	17.60
ATOM	1404	C	THR	183	7.499	5.949	-2.214	1.00	17.60
ATOM	1405	O	THR	183	8.115	4.907	-2.484	1.00	17.60
ATOM	1406	N	ASP	184	7.928	7.121	-2.695	1.00	17.60
ATOM	1407	CA	ASP	184	9.237	7.211	-3.312	1.00	17.60
ATOM	1408	CB	ASP	184	10.358	7.007	-2.297	1.00	17.60
ATOM	1409	CG	ASP	184	11.696	7.629	-2.733	1.00	17.60
ATOM	1410	OD1	ASP	184	12.108	8.669	-2.169	1.00	17.60
ATOM	1411	OD2	ASP	184	12.327	7.064	-3.641	1.00	17.60
ATOM	1412	C	ASP	184	9.512	6.249	-4.437	1.00	17.60
ATOM	1413	O	ASP	184	9.890	5.099	-4.301	1.00	17.60
ATOM	1414	N	PHE	185	9.406	6.906	-5.558	1.00	17.60
ATOM	1415	CA	PHE	185	9.612	6.360	-6.849	1.00	17.60
ATOM	1416	CB	PHE	185	8.399	6.721	-7.705	1.00	17.60
ATOM	1417	CG	PHE	185	7.425	5.604	-7.618	1.00	17.60
ATOM	1418	CD1	PHE	185	7.330	4.778	-8.693	1.00	17.60
ATOM	1419	CD2	PHE	185	6.823	5.352	-6.419	1.00	17.60
ATOM	1420	CE1	PHE	185	6.631	3.635	-8.532	1.00	17.60
ATOM	1421	CE2	PHE	185	6.316	4.196	-6.264	1.00	17.60
ATOM	1422	CZ	PHE	185	6.034	3.346	-7.319	1.00	17.60
ATOM	1423	C	PHE	185	10.888	6.918	-7.409	1.00	17.60
ATOM	1424	O	PHE	185	11.080	6.965	-8.622	1.00	17.60
ATOM	1425	N	GLY	186	11.794	7.360	-6.533	1.00	17.60
ATOM	1426	CA	GLY	186	13.047	8.013	-6.900	1.00	17.60
ATOM	1427	C	GLY	186	13.804	7.255	-7.955	1.00	17.60

ATOM	1428	O	GLY	186	14.366	7.915	-8.807	1.00	17.60
ATOM	1429	N	PHE	187	13.897	5.919	-8.007	1.00	17.60
ATOM	1430	CA	PHE	187	14.601	5.365	-9.122	1.00	17.60
ATOM	1431	CB	PHE	187	15.637	4.456	-8.587	1.00	17.60
ATOM	1432	CG	PHE	187	16.700	5.284	-7.956	1.00	17.60
ATOM	1433	CD1	PHE	187	17.179	6.419	-8.520	1.00	17.60
ATOM	1434	CD2	PHE	187	17.191	4.966	-6.761	1.00	17.60
ATOM	1435	CE1	PHE	187	18.042	7.225	-7.889	1.00	17.60
ATOM	1436	CE2	PHE	187	18.103	5.731	-6.110	1.00	17.60
ATOM	1437	CZ	PHE	187	18.537	6.889	-6.670	1.00	17.60
ATOM	1438	C	PHE	187	13.699	4.673	-10.094	1.00	17.60
ATOM	1439	O	PHE	187	14.208	3.926	-10.910	1.00	17.60
ATOM	1440	N	ALA	188	12.385	4.917	-10.091	1.00	17.60
ATOM	1441	CA	ALA	188	11.455	4.171	-10.917	1.00	17.60
ATOM	1442	CB	ALA	188	10.072	4.600	-10.621	1.00	17.60
ATOM	1443	C	ALA	188	11.737	4.425	-12.371	1.00	17.60
ATOM	1444	O	ALA	188	12.142	5.520	-12.669	1.00	17.60
ATOM	1445	N	LYS	189	11.611	3.537	-13.330	1.00	17.60
ATOM	1446	CA	LYS	189	11.986	3.831	-14.684	1.00	17.60
	1447	CB	LYS	189	13.532	3.536	-14.873	1.00	17.60
	1448	CG	LYS	189	14.124	3.832	-16.269	1.00	17.60
ATOM	1449	CD	LYS	189	15.612	3.934	-16.303	1.00	17.60
ATOM	1450	CE	LYS	189	16.128	4.237	-17.690	1.00	17.60
ATOM	1451	NZ	LYS	189	15.663	5.500	-18.226	1.00	17.60
ATOM	1452	C	LYS	189	11.124	2.966	-15.569	1.00	17.60
ATOM	1453	O	LYS	189	10.911	1.801	-15.243	1.00	17.60
ATOM	1454	N	ARG	190	10.559	3.539	-16.639	1.00	17.60
ATOM	1455	CA	ARG	190	9.803	2.726	-17.556	1.00	17.60
ATOM	1456	CB	ARG	190	8.757	3.613	-18.208	1.00	17.60
ATOM	1457	CG	ARG	190	7.847	2.691	-19.029	1.00	17.60
ATOM	1458	CD	ARG	190	6.387	3.051	-19.316	1.00	17.60
ATOM	1459	NE	ARG	190	6.243	2.826	-20.731	1.00	17.60
ATOM	1460	CZ	ARG	190	5.277	2.166	-21.314	1.00	17.60
ATOM	1461	NH1	ARG	190	4.285	1.604	-20.639	1.00	17.60
ATOM	1462	NH2	ARG	190	5.353	2.118	-22.627	1.00	17.60
ATOM	1463	C	ARG	190	10.819	2.181	-18.542	1.00	17.60
ATOM	1464	O	ARG	190	11.256	2.944	-19.388	1.00	17.60
ATOM	1465	N	VAL	191	11.324	0.968	-18.484	1.00	17.60
ATOM	1466	CA	VAL	191	12.278	0.554	-19.480	1.00	17.60
ATOM	1467	CB	VAL	191	13.690	0.066	-19.118	1.00	17.60
ATOM	1468	CG1	VAL	191	14.404	1.268	-18.794	1.00	17.60
ATOM	1469	CG2	VAL	191	13.845	-0.861	-17.946	1.00	17.60
ATOM	1470	C	VAL	191	11.722	-0.691	-20.031	1.00	17.60
ATOM	1471	O	VAL	191	11.328	-1.638	-19.334	1.00	17.60
	1472	N	LYS	192	11.757	-0.678	-21.355	1.00	17.60
A.	1473	CA	LYS	192	11.285	-1.863	-22.010	1.00	17.60
ATOM	1474	CB	LYS	192	10.357	-1.486	-23.144	1.00	17.60
ATOM	1475	CG	LYS	192	9.499	-2.664	-23.563	1.00	17.60
ATOM	1476	CD	LYS	192	8.442	-2.036	-24.415	1.00	17.60
ATOM	1477	CE	LYS	192	7.131	-1.896	-23.730	1.00	17.60
ATOM	1478	NZ	LYS	192	7.259	-1.140	-22.516	1.00	17.60
ATOM	1479	C	LYS	192	12.492	-2.606	-22.499	1.00	17.60
ATOM	1480	O	LYS	192	12.485	-3.040	-23.629	1.00	17.60
ATOM	1481	N	GLY	193	13.521	-2.824	-21.676	1.00	17.60
ATOM	1482	CA	GLY	193	14.720	-3.524	-22.136	1.00	17.60
ATOM	1483	C	GLY	193	15.583	-3.781	-20.927	1.00	17.60
ATOM	1484	O	GLY	193	15.118	-4.209	-19.852	1.00	17.60
ATOM	1485	N	ARG	194	16.823	-3.393	-21.137	1.00	17.60
ATOM	1486	CA	ARG	194	17.878	-3.572	-20.168	1.00	17.60
ATOM	1487	CB	ARG	194	19.034	-4.371	-20.795	1.00	17.60
ATOM	1488	CG	ARG	194	18.836	-4.889	-22.302	1.00	17.60
ATOM	1489	CD	ARG	194	19.128	-3.977	-23.579	1.00	17.60
ATOM	1490	NE	ARG	194	18.904	-2.529	-23.379	1.00	17.60
ATOM	1491	CZ	ARG	194	19.206	-1.549	-24.258	1.00	17.60
ATOM	1492	NH1	ARG	194	19.757	-1.773	-25.484	1.00	17.60
ATOM	1493	NH2	ARG	194	19.008	-0.285	-23.816	1.00	17.60
ATOM	1494	C	ARG	194	18.297	-2.153	-19.039	1.00	17.60
ATOM	1495	O	ARG	194	18.018	-1.255	-20.639	1.00	17.60
ATOM	1496	N	THR	195	18.878	-1.851	-18.683	1.00	17.60
ATOM	1497	CA	THR	195	19.282	-0.494	-18.361	1.00	17.60
ATOM	1498	CB	THR	195	18.109	0.233	-17.582	1.00	17.60
ATOM	1499	OG1	THR	195	18.490	1.592	-17.454	1.00	17.60
ATOM	1500	CG2	THR	195	17.799	-0.356	-16.218	1.00	17.60
ATOM	1501	C	THR	195	20.561	-0.687	-17.539	1.00	17.60
ATOM	1502	O	THR	195	20.950	-1.823	-17.194	1.00	17.60
ATOM	1503	N	TRP	196	21.207	0.447	-17.274	1.00	17.60
ATOM	1504	CA	TRP	196	22.534	0.428	-16.720	1.00	17.60
ATOM	1505	CB	TRP	196	23.543	0.692	-17.876	1.00	17.60
ATOM	1506	CG	TRP	196	23.765	-0.441	-18.861	1.00	17.60
ATOM	1507	CD2	TRP	196	23.156	-0.589	-20.050	1.00	17.60
ATOM	1508	CE2	TRP	196	23.633	-1.818	-20.452	1.00	17.60
ATOM	1509	CE3	TRP	196	22.265	0.119	-20.841	1.00	17.60
ATOM	1510	CD1	TRP	196	24.571	-1.492	-18.571	1.00	17.60
ATOM	1511	NE1	TRP	196	24.459	-2.321	-19.557	1.00	17.60
ATOM	1512	CZ2	TRP	196	23.249	-2.394	-21.635	1.00	17.60
ATOM	1513	CZ3	TRP	196	21.867	-0.465	-22.047	1.00	17.60
ATOM	1514	CH2	TRP	196	22.355	-1.708	-22.431	1.00	17.60
ATOM	1515	C	TRP	196	22.823	1.384	-15.562	1.00	17.60
ATOM	1516	O	TRP	196	23.992	1.548	-15.192	1.00	17.60
ATOM	1517	N	THR	197	21.863	2.032	-14.916	1.00	17.60
ATOM	1518	CA	THR	197	22.282	2.964	-13.888	1.00	17.60
ATOM	1519	CB	THR	197	21.137	3.911	-13.599	1.00	17.60
ATOM	1520	OG1	THR	197	20.785	4.568	-14.800	1.00	17.60
ATOM	1521	RD	THR	197	19.406	4.308	-15.392	1.00	17.60
ATOM	1522	OE1	THR	197	19.303	4.976	-16.676	1.00	17.60
ATOM	1523	OE2	THR	197	19.173	2.875	-15.341	1.00	17.60
ATOM	1524	OE3	THR	197	18.398	5.000	-14.424	1.00	17.60
ATOM	1525	CG2	THR	197	21.529	4.965	-12.542	1.00	17.60
ATOM	1526	C	THR	197	22.722	2.265	-12.614	1.00	17.60
ATOM	1527	O	THR	197	22.056	1.332	-12.218	1.00	17.60
ATOM	1528	N	LEU	198	23.820	2.581	-11.937	1.00	17.60
ATOM	1529	CA	LEU	198	24.011	1.956	-10.630	1.00	17.60
ATOM	1530	CB	LEU	198	25.457	1.920	-10.093	1.00	17.60
ATOM	1531	CG	LEU	198	25.790	1.029	-8.844	1.00	17.60
ATOM	1532	CD1	LEU	198	26.706	-0.165	-9.175	1.00	17.60
ATOM	1533	CD2	LEU	198	26.508	1.905	-7.827	1.00	17.60
ATOM	1534	C	LEU	198	23.235	2.864	-9.714	1.00	17.60
ATOM	1535	O	LEU	198	23.519	4.056	-9.639	1.00	17.60
ATOM	1536	N	CSH	199	22.164	2.345	-9.157	1.00	17.60
ATOM	1537	CA	CSH	199	21.362	3.034	-8.179	1.00	17.60
ATOM	1538	CB	CSH	199	20.496	4.099	-8.872	1.00	17.60
ATOM	1539	SG	CSH	199	19.489	3.416	-10.182	1.00	17.60
ATOM	1540	C	CSH	199	20.512	1.939	-7.527	1.00	17.60
ATOM	1541	O	CSH	199	20.264	0.867	-8.150	1.00	17.60
ATOM	1542	N	GLY	200	20.212	2.238	-6.235	1.00	17.60
ATOM	1543	CA	GLY	200	19.421	1.400	-5.333	1.00	17.60
ATOM	1544	C	GLY	200	19.950	1.655	-3.920	1.00	17.60
ATOM	1545	O	GLY	200	20.649	2.665	-3.762	1.00	17.60
ATOM	1546	N	THR	201	19.715	0.871	-2.871	1.00	17.60
ATOM	1547	CA	THR	201	20.327	1.170	-1.581	1.00	17.60
ATOM	1548	CB	THR	201	19.230	1.276	-0.488	1.00	17.60
ATOM	1549	OG1	THR	201	18.496	2.469	-0.759	1.00	17.60
ATOM	1550	CG2	THR	201	19.781	1.241	0.922	1.00	17.60
ATOM	1551	C	THR	201	21.298	0.045	-1.279	1.00	17.60
ATOM	1552	O	THR	201	20.880	-1.094	-1.352	1.00	17.60
ATOM	1553	N	PRO	202	22.546	0.199	-0.914	1.00	17.60
ATOM	1554	CD	PRO	202	23.092	1.469	-0.483	1.00	17.60
ATOM	1555	CA	PRO	202	23.543	-0.866	-0.870	1.00	17.60
ATOM	1556	CB	PRO	202	24.616	-0.340	0.037	1.00	17.60
ATOM	1557	CG	PRO	202	24.570	1.114	-0.345	1.00	17.60

ATOM	1558	C	PRO	202	23.157	-2.268	-0.480	1.00	17.60
ATOM	1559	O	PRO	202	23.356	-3.157	-1.270	1.00	17.60
ATOM	1560	N	GLU	203	22.525	-2.581	0.646	1.00	17.60
ATOM	1561	CA	GLU	203	22.258	-3.989	0.997	1.00	17.60
ATOM	1562	CB	GLU	203	21.902	-4.183	2.507	1.00	17.60
ATOM	1563	CG	GLU	203	21.311	-3.024	3.263	1.00	17.60
ATOM	1564	CD	GLU	203	22.311	-1.998	3.776	1.00	17.60
ATOM	1565	OE1	GLU	203	22.769	-2.189	4.899	1.00	17.60
ATOM	1566	OE2	GLU	203	22.597	-1.002	3.099	1.00	17.60
ATOM	1567	C	GLU	203	21.155	-4.641	0.199	1.00	17.60
ATOM	1568	O	GLU	203	20.910	-5.851	0.231	1.00	17.60
ATOM	1569	N	TYR	204	20.484	-3.743	-0.506	1.00	17.60
ATOM	1570	CA	TYR	204	19.383	-4.131	-1.320	1.00	17.60
ATOM	1571	CB	TYR	204	18.334	-2.999	-1.302	1.00	17.60
ATOM	1572	CG	TYR	204	17.497	-3.272	-0.063	1.00	17.60
ATOM	1573	CD1	TYR	204	16.576	-4.312	-0.091	1.00	17.60
ATOM	1574	CE1	TYR	204	15.933	-4.696	1.078	1.00	17.60
ATOM	1575	CD2	TYR	204	17.766	-2.601	1.142	1.00	17.60
ATOM	1576	CE2	TYR	204	17.096	-2.995	2.309	1.00	17.60
[illegible]	1577	CZ	TYR	204	16.201	-4.043	2.265	1.00	17.60
[illegible]	1578	OH	TYR	204	15.581	-4.452	3.408	1.00	17.60
ATOM	1579	C	TYR	204	19.877	-4.427	-2.708	1.00	17.60
ATOM	1580	O	TYR	204	19.171	-5.307	-3.439	1.00	17.60
ATOM	1581	N	LEU	205	21.077	-3.985	-3.124	1.00	17.60
ATOM	1582	CA	LEU	205	21.511	-4.134	-4.497	1.00	17.60
ATOM	1583	CB	LEU	205	22.860	-3.478	-4.804	1.00	17.60
ATOM	1584	CG	LEU	205	23.128	-2.133	-5.266	1.00	17.60
ATOM	1585	CD1	LEU	205	21.859	-1.372	-5.202	1.00	17.60
ATOM	1586	CD2	LEU	205	24.309	-1.460	-4.622	1.00	17.60
ATOM	1587	C	LEU	205	21.559	-5.594	-4.918	1.00	17.60
ATOM	1588	O	LEU	205	21.856	-6.489	-4.127	1.00	17.60
ATOM	1589	N	ALA	206	21.087	-5.838	-6.143	1.00	17.60
ATOM	1590	CA	ALA	206	21.160	-7.153	-6.746	1.00	17.60
ATOM	1591	CB	ALA	206	20.188	-7.216	-7.850	1.00	17.60
ATOM	1592	C	ALA	206	22.556	-7.266	-7.296	1.00	17.60
ATOM	1593	O	ALA	206	23.043	-6.155	-7.645	1.00	17.60
ATOM	1594	N	PRO	207	23.262	-8.404	-7.472	1.00	17.60
ATOM	1595	CD	PRO	207	22.622	-9.695	-7.672	1.00	17.60
ATOM	1596	CA	PRO	207	24.675	-8.524	-7.827	1.00	17.60
ATOM	1597	CB	PRO	207	25.063	-9.914	-7.546	1.00	17.60
ATOM	1598	CG	PRO	207	23.756	-10.662	-7.352	1.00	17.60
ATOM	1599	C	PRO	207	24.999	-8.193	-9.289	1.00	17.60
ATOM	1600	O	PRO	207	26.123	-7.789	-9.592	1.00	17.60
ATOM	1601	N	GLU	208	24.034	-8.322	-10.214	1.00	17.60
	1602	CA	GLU	208	24.253	-7.872	-11.546	1.00	17.60
	1603	CB	GLU	208	23.118	-8.277	-12.480	1.00	17.60
ATOM	1604	CG	GLU	208	21.773	-7.703	-12.166	1.00	17.60
ATOM	1605	CD	GLU	208	20.791	-8.657	-11.532	1.00	17.60
ATOM	1606	OE1	GLU	208	19.582	-8.489	-11.672	1.00	17.60
ATOM	1607	OE2	GLU	208	21.237	-9.593	-10.890	1.00	17.60
ATOM	1608	C	GLU	208	24.369	-6.368	-11.527	1.00	17.60
ATOM	1609	O	GLU	208	24.954	-5.809	-12.441	1.00	17.60
ATOM	1610	N	ILE	209	23.881	-5.605	-10.563	1.00	17.60
ATOM	1611	CA	ILE	209	24.037	-4.178	-10.681	1.00	17.60
ATOM	1612	CB	ILE	209	23.019	-3.466	-9.826	1.00	17.60
ATOM	1613	CG2	ILE	209	23.132	-1.955	-9.969	1.00	17.60
ATOM	1614	CG1	ILE	209	21.656	-3.963	-10.252	1.00	17.60
ATOM	1615	CD1	ILE	209	20.589	-3.274	-9.398	1.00	17.60
ATOM	1616	C	ILE	209	25.419	-3.790	-10.264	1.00	17.60
ATOM	1617	O	ILE	209	25.930	-2.849	-10.853	1.00	17.60
ATOM	1618	N	ILE	210	26.065	-4.445	-9.290	1.00	17.60
ATOM	1619	CA	ILE	210	27.371	-3.929	-8.925	1.00	17.60
ATOM	1620	CB	ILE	210	27.675	-4.023	-7.360	1.00	17.60
ATOM	1621	CG2	ILE	210	26.613	-4.151	-6.511	1.00	17.60
ATOM	1622	CG1	ILE	210	28.514	-5.238	-7.062	1.00	17.60
ATOM	1623	CD1	ILE	210	29.662	-5.033	-6.015	1.00	17.60
ATOM	1624	C	ILE	210	26.381	-4.708	-9.764	1.00	17.60
ATOM	1625	O	ILE	210	29.456	-4.186	-10.090	1.00	17.60
ATOM	1626	N	LEU	211	28.186	-5.966	-10.156	1.00	17.60
ATOM	1627	CA	LEU	211	29.045	-6.491	-11.203	1.00	17.60
ATOM	1628	CB	LEU	211	28.979	-7.970	-11.168	1.00	17.60
ATOM	1629	CG	LEU	211	30.036	-8.790	-10.509	1.00	17.60
ATOM	1630	CD1	LEU	211	31.005	-7.998	-9.705	1.00	17.60
ATOM	1631	CD2	LEU	211	29.239	-9.772	-9.709	1.00	17.60
ATOM	1632	C	LEU	211	28.310	-5.930	-12.426	1.00	17.60
ATOM	1633	O	LEU	211	27.566	-6.706	-13.033	1.00	17.60
ATOM	1634	N	SER	212	28.460	-4.643	-12.792	1.00	17.60
ATOM	1635	CA	SER	212	27.570	-3.987	-13.749	1.00	17.60
ATOM	1636	CB	SER	212	27.958	-2.495	-13.812	1.00	17.60
ATOM	1637	OG	SER	212	29.350	-2.346	-13.703	1.00	17.60
ATOM	1638	C	SER	212	27.352	-4.508	-15.174	1.00	17.60
ATOM	1639	O	SER	212	28.027	-4.155	-16.132	1.00	17.60
ATOM	1640	N	LYS	213	26.355	-5.367	-15.333	1.00	17.60
ATOM	1641	CA	LYS	213	26.003	-6.307	-16.542	1.00	17.60
ATOM	1642	CB	LYS	213	26.000	-7.577	-16.147	1.00	17.60
ATOM	1643	CG	LYS	213	27.382	-8.055	-15.687	1.00	17.60
ATOM	1644	CD	LYS	213	27.370	-9.316	-14.813	1.00	17.60
ATOM	1645	CE	LYS	213	26.464	-10.378	-15.409	1.00	17.60
ATOM	1646	NZ	LYS	213	26.696	-11.666	-14.795	1.00	17.60
ATOM	1647	C	LYS	213	24.655	-5.740	-17.235	1.00	17.60
ATOM	1648	O	LYS	213	24.246	-6.439	-18.186	1.00	17.60
ATOM	1649	N	GLY	214	23.926	-4.657	-16.893	1.00	17.60
ATOM	1650	CA	GLY	214	22.655	-4.464	-17.551	1.00	17.60
ATOM	1651	C	GLY	214	21.666	-5.376	-16.859	1.00	17.60
ATOM	1652	O	GLY	214	21.833	-6.585	-16.683	1.00	17.60
ATOM	1653	N	TYR	215	20.614	-4.688	-16.458	1.00	17.60
ATOM	1654	CA	TYR	215	19.646	-5.310	-15.619	1.00	17.60
ATOM	1655	CB	TYR	215	19.957	-4.883	-14.156	1.00	17.60
ATOM	1656	CG	TYR	215	20.034	-3.384	-13.771	1.00	17.60
ATOM	1657	CD1	TYR	215	18.955	-2.853	-13.164	1.00	17.60
ATOM	1658	CE1	TYR	215	18.911	-1.569	-12.743	1.00	17.60
ATOM	1659	CD2	TYR	215	21.120	-2.563	-13.960	1.00	17.60
ATOM	1660	CE2	TYR	215	21.081	-1.228	-13.542	1.00	17.60
ATOM	1661	CZ	TYR	215	19.949	-0.758	-12.930	1.00	17.60
ATOM	1662	OH	TYR	215	19.756	0.537	-12.505	1.00	17.60
ATOM	1663	C	TYR	215	18.269	-4.930	-16.107	1.00	17.60
ATOM	1664	O	TYR	215	18.007	-4.081	-16.966	1.00	17.60
ATOM	1665	N	ASN	216	17.345	-5.574	-15.475	1.00	17.60
ATOM	1666	CA	ASN	216	15.985	-5.309	-15.915	1.00	17.60
ATOM	1667	CB	ASN	216	15.806	-6.618	-16.901	1.00	17.60
ATOM	1668	CG	ASN	216	16.398	-7.924	-16.334	1.00	17.60
ATOM	1669	OD1	ASN	216	16.693	-8.078	-15.132	1.00	17.60
ATOM	1670	ND2	ASN	216	16.658	-8.884	-17.198	1.00	17.60
ATOM	1671	C	ASN	216	15.153	-5.753	-14.669	1.00	17.60
ATOM	1672	O	ASN	216	15.663	-5.836	-13.540	1.00	17.60
ATOM	1673	N	LYS	217	13.889	-6.036	-14.944	1.00	17.60
ATOM	1674	CA	LYS	217	12.852	-6.326	-13.994	1.00	17.60
ATOM	1675	CB	LYS	217	11.612	-7.037	-14.631	1.00	17.60
ATOM	1676	CG	LYS	217	11.066	-6.652	-16.021	1.00	17.60
ATOM	1677	CD	LYS	217	10.678	-5.164	-16.061	1.00	17.60
ATOM	1678	CE	LYS	217	11.315	-4.316	-17.221	1.00	17.60
ATOM	1679	NZ	LYS	217	12.779	-4.482	-17.387	1.00	17.60
ATOM	1680	C	LYS	217	13.337	-7.246	-12.914	1.00	17.60
ATOM	1681	O	LYS	217	12.702	-7.150	-11.869	1.00	17.60
ATOM	1682	N	ALA	218	14.381	-8.079	-13.100	1.00	17.60
ATOM	1683	CA	ALA	218	14.771	-9.089	-12.135	1.00	17.60
ATOM	1684	CB	ALA	218	15.675	-10.083	-12.804	1.00	17.60
ATOM	1685	C	ALA	218	15.462	-8.567	-10.886	1.00	17.60
ATOM	1686	O	ALA	218	15.548	-9.254	-9.850	1.00	17.60
ATOM	1687	N	VAL	219	15.901	-7.300	-10.952	1.00	17.60

ATOM	1688	CA	VAL	219	16.693	-6.689	-9.787	1.00	17.60
ATOM	1689	CB	VAL	219	17.088	-5.299	-9.997	1.00	17.60
ATOM	1690	CG1	VAL	219	18.382	-5.527	-10.951	1.00	17.60
ATOM	1691	CG2	VAL	219	16.118	-4.231	-10.675	1.00	17.60
ATOM	1692	C	VAL	219	15.420	-6.511	-8.736	1.00	17.60
ATOM	1693	O	VAL	219	15.682	-6.634	-7.532	1.00	17.60
ATOM	1694	N	ASP	220	14.382	-6.314	-9.165	1.00	17.60
ATOM	1695	CA	ASP	220	13.121	-6.116	-8.226	1.00	17.60
ATOM	1696	CB	ASP	220	11.862	-5.622	-8.950	1.00	17.60
ATOM	1697	CG	ASP	220	11.891	-4.095	-9.382	1.00	17.60
ATOM	1698	OD1	ASP	220	12.629	-3.655	-10.036	1.00	17.60
ATOM	1699	OD2	ASP	220	11.183	-3.318	-8.536	1.00	17.60
ATOM	1700	C	ASP	220	12.855	-7.400	-7.693	1.00	17.60
ATOM	1701	O	ASP	220	12.293	-7.339	-6.404	1.00	17.60
ATOM	1702	N	TRP	221	13.275	-8.568	-7.964	1.00	17.60
ATOM	1703	CA	TRP	221	12.892	-9.736	-7.235	1.00	17.60
ATOM	1704	CB	TRP	221	12.618	-10.867	-8.137	1.00	17.60
ATOM	1705	CG	TRP	221	11.309	-10.554	-8.782	1.00	17.60
ATOM	1706	CD2	TRP	221	10.063	-10.346	-8.240	1.00	17.60
	1707	CE2	TRP	221	9.339	-10.089	-9.383	1.00	17.60
.	1708	CE3	TRP	221	9.373	-10.317	-7.052	1.00	17.60
ATOM	1709	CD1	TRP	221	11.349	-10.436	-10.106	1.00	17.60
ATOM	1710	NE1	TRP	221	10.126	-10.155	-10.432	1.00	17.60
ATOM	1711	CE2	TRP	221	7.994	-9.810	-9.433	1.00	17.60
ATOM	1712	CE3	TRP	221	8.005	-10.037	-7.070	1.00	17.60
ATOM	1713	CH2	TRP	221	7.312	-9.786	-8.241	1.00	17.60
ATOM	1714	C	TRP	221	13.947	-10.105	-6.287	1.00	17.60
ATOM	1715	O	TRP	221	13.571	-10.661	-5.248	1.00	17.60
ATOM	1716	N	TRP	222	15.207	-9.748	-6.595	1.00	17.60
ATOM	1717	CA	TRP	222	16.292	-9.946	-5.628	1.00	17.60
ATOM	1718	CB	TRP	222	17.644	-9.488	-6.138	1.00	17.60
ATOM	1719	CG	TRP	222	18.822	-9.618	-5.173	1.00	17.60
ATOM	1720	CD2	TRP	222	19.762	-10.596	-5.142	1.00	17.60
ATOM	1721	CE2	TRP	222	20.642	-10.327	-4.192	1.00	17.60
ATOM	1722	CE3	TRP	222	20.024	-11.777	-5.757	1.00	17.60
ATOM	1723	CD1	TRP	222	19.125	-8.637	-4.272	1.00	17.60
ATOM	1724	NE1	TRP	222	20.249	-8.957	-3.691	1.00	17.60
ATOM	1725	CZ2	TRP	222	21.779	-10.825	-3.855	1.00	17.60
ATOM	1726	CZ3	TRP	222	21.165	-12.481	-5.423	1.00	17.60
ATOM	1727	CH2	TRP	222	22.042	-12.018	-4.482	1.00	17.60
ATOM	1728	C	TRP	222	15.947	-9.088	-4.419	1.00	17.60
ATOM	1729	O	TRP	222	15.795	-9.674	-3.342	1.00	17.60
ATOM	1730	N	ALA	223	15.760	-7.761	-4.538	1.00	17.60
ATOM	1731	CA	ALA	223	15.375	-6.950	-3.399	1.00	17.60
'	1732	CB	ALA	223	15.327	-5.547	-3.843	1.00	17.60
)	1733	C	ALA	223	14.315	-7.495	-2.705	1.00	17.60
ATOM	1734	O	ALA	223	14.301	-7.476	-1.482	1.00	17.60
ATOM	1735	N	LEU	224	13.069	-8.096	-3.274	1.00	17.60
ATOM	1736	CA	LEU	224	11.974	-8.685	-2.486	1.00	17.60
ATOM	1737	CB	LEU	224	10.937	-9.485	-3.241	1.00	17.60
ATOM	1738	CG	LEU	224	9.485	-9.501	-2.844	1.00	17.60
ATOM	1739	CD1	LEU	224	8.965	-10.836	-3.302	1.00	17.60
ATOM	1740	CD2	LEU	224	9.261	-9.281	-1.373	1.00	17.60
ATOM	1741	C	LEU	224	12.550	-9.740	-1.578	1.00	17.60
ATOM	1742	O	LEU	224	12.169	-9.823	-0.424	1.00	17.60
ATOM	1743	N	GLY	225	13.476	-10.529	-2.085	1.00	17.60
ATOM	1744	CA	GLY	225	14.103	-11.542	-1.294	1.00	17.60
ATOM	1745	C	GLY	225	14.813	-10.920	-0.130	1.00	17.60
ATOM	1746	O	GLY	225	14.956	-11.540	0.918	1.00	17.60
ATOM	1747	N	VAL	226	15.224	-9.667	-0.270	1.00	17.60
ATOM	1748	CA	VAL	226	15.967	-9.059	0.807	1.00	17.60
ATOM	1749	CB	VAL	226	16.941	-8.040	0.214	1.00	17.60
ATOM	1750	CG1	VAL	226	17.879	-7.675	1.347	1.00	17.60
ATOM	1751	CG2	VAL	226	17.842	-8.600	-0.901	1.00	17.60
ATOM	1752	C	VAL	226	14.987	-8.492	1.772	1.00	17.60
ATOM	1753	O	VAL	226	15.122	-8.756	2.945	1.00	17.60
ATOM	1754	N	LEU	227	13.935	-7.855	1.335	1.00	17.60
ATOM	1755	CA	LEU	227	12.927	-7.604	2.235	1.00	17.60
ATOM	1756	CB	LEU	227	11.758	-6.862	1.546	1.00	17.60
ATOM	1757	CG	LEU	227	10.845	-6.168	2.472	1.00	17.60
ATOM	1758	CD1	LEU	227	11.431	-4.853	2.831	1.00	17.60
ATOM	1759	CD2	LEU	227	9.557	-5.881	1.814	1.00	17.60
ATOM	1760	C	LEU	227	12.429	-8.573	3.039	1.00	17.60
ATOM	1761	O	LEU	227	12.454	-8.492	4.255	1.00	17.60
ATOM	1762	N	ILE	228	12.066	-9.708	2.468	1.00	17.60
ATOM	1763	CA	ILE	228	11.512	-10.836	3.225	1.00	17.60
ATOM	1764	CB	ILE	228	11.323	-12.015	2.287	1.00	17.60
ATOM	1765	CG2	ILE	228	10.621	-13.152	3.335	1.00	17.60
ATOM	1766	CG1	ILE	228	9.973	-11.655	1.361	1.00	17.60
ATOM	1767	CD1	ILE	228	9.646	-12.704	0.299	1.00	17.60
ATOM	1768	C	ILE	228	12.505	-11.325	4.256	1.00	17.60
ATOM	1769	O	ILE	228	12.083	-11.662	5.361	1.00	17.60
ATOM	1770	N	TYR	229	13.797	-11.388	4.025	1.00	17.60
ATOM	1771	CA	TYR	229	14.755	-11.843	4.987	1.00	17.60
ATOM	1772	CB	TYR	229	16.053	-12.035	4.312	1.00	17.60
ATOM	1773	CG	TYR	229	17.190	-12.623	5.093	1.00	17.60
ATOM	1774	CD1	TYR	229	17.769	-12.048	6.189	1.00	17.60
ATOM	1775	CE1	TYR	229	18.879	-12.635	6.743	1.00	17.60
ATOM	1776	CD2	TYR	229	17.708	-13.784	4.578	1.00	17.60
ATOM	1777	CE2	TYR	229	18.803	-14.386	5.125	1.00	17.60
ATOM	1778	CZ	TYR	229	19.388	-13.795	6.194	1.00	17.60
ATOM	1779	OH	TYR	229	20.573	-14.356	6.616	1.00	17.60
ATOM	1780	C	TYR	229	14.891	-10.782	6.046	1.00	17.60
ATOM	1781	O	TYR	229	14.986	-11.107	7.228	1.00	17.60
ATOM	1782	N	GLU	230	14.916	-9.511	5.676	1.00	17.60
ATOM	1783	CA	GLU	230	15.215	-8.438	6.591	1.00	17.60
ATOM	1784	CB	GLU	230	15.285	-7.201	5.656	1.00	17.60
ATOM	1785	CG	GLU	230	15.172	-5.709	6.007	1.00	17.60
ATOM	1786	CD	GLU	230	16.309	-4.864	6.559	1.00	17.60
ATOM	1787	OE1	GLU	230	17.092	-4.267	5.813	1.00	17.60
ATOM	1788	OE2	GLU	230	16.353	-4.754	7.773	1.00	17.60
ATOM	1789	C	GLU	230	14.158	-8.448	7.669	1.00	17.60
ATOM	1790	O	GLU	230	14.463	-8.531	8.865	1.00	17.60
ATOM	1791	N	MET	231	12.910	-8.506	7.203	1.00	17.60
ATOM	1792	CA	MET	231	11.754	-8.524	8.073	1.00	17.60
ATOM	1793	CB	MET	231	10.508	-8.581	7.237	1.00	17.60
ATOM	1794	CG	MET	231	10.214	-7.355	6.413	1.00	17.60
ATOM	1795	SD	MET	231	8.603	-7.416	5.592	1.00	17.60
ATOM	1796	CE	MET	231	9.024	-8.484	4.278	1.00	17.60
ATOM	1797	C	MET	231	11.783	-9.700	9.029	1.00	17.60
ATOM	1798	O	MET	231	11.784	-9.434	10.207	1.00	17.60
ATOM	1799	N	ALA	232	11.849	-10.972	8.621	1.00	17.60
ATOM	1800	CA	ALA	232	11.867	-12.131	9.508	1.00	17.60
ATOM	1801	CB	ALA	232	11.626	-13.428	8.744	1.00	17.60
ATOM	1802	C	ALA	232	13.133	-12.352	10.303	1.00	17.60
ATOM	1803	O	ALA	232	13.076	-12.872	11.426	1.00	17.60
ATOM	1804	N	ALA	233	14.306	-12.048	9.752	1.00	17.60
ATOM	1805	CA	ALA	233	15.523	-12.212	10.519	1.00	17.60
ATOM	1806	CB	ALA	233	16.732	-12.390	9.667	1.00	17.60
ATOM	1807	C	ALA	233	15.874	-11.065	11.426	1.00	17.60
ATOM	1808	O	ALA	233	16.606	-11.314	12.371	1.00	17.60
ATOM	1809	N	GLY	234	15.425	-9.830	11.189	1.00	17.60
ATOM	1810	CA	GLY	234	15.777	-8.652	12.007	1.00	17.60
ATOM	1811	C	GLY	234	16.903	-7.776	11.438	1.00	17.60
ATOM	1812	O	GLY	234	17.185	-6.645	11.864	1.00	17.60
ATOM	1813	N	TYR	235	17.544	-8.336	10.415	1.00	17.60
ATOM	1814	CA	TYR	235	18.657	-7.705	9.737	1.00	17.60
ATOM	1815	CB	TYR	235	19.921	-7.936	10.566	1.00	17.60
ATOM	1816	CG	TYR	235	20.159	-9.387	10.834	1.00	17.60
ATOM	1817	CD1	TYR	235	19.731	-9.817	12.043	1.00	17.60

ATOM	1818	CE1	TYR	235	19.864	-11.132	12.322	1.00 17.60
ATOM	1819	CD2	TYR	235	20.710	-10.222	9.880	1.00 17.60
ATOM	1820	CE2	TYR	235	20.824	-11.549	10.353	1.00 17.60
ATOM	1821	CZ	TYR	235	20.378	-11.957	11.393	1.00 17.60
ATOM	1822	OH	TYR	235	20.512	-13.250	11.795	1.00 17.60
ATOM	1823	C	TYR	235	16.889	-8.172	8.273	1.00 17.60
ATOM	1824	O	TYR	235	18.316	-9.177	7.841	1.00 17.60
ATOM	1825	N	PRO	236	19.715	-7.471	7.462	1.00 17.60
ATOM	1826	CD	PRO	236	20.383	-6.191	7.706	1.00 17.60
ATOM	1827	CA	PRO	236	19.963	-7.777	6.097	1.00 17.60
ATOM	1828	CB	PRO	236	20.765	-6.562	5.688	1.00 17.60
ATOM	1829	CG	PRO	236	20.254	-5.412	6.426	1.00 17.60
ATOM	1830	C	PRO	236	20.667	-9.112	6.038	1.00 17.60
ATOM	1831	O	PRO	236	21.267	-9.553	7.025	1.00 17.60
ATOM	1832	N	PRO	237	20.583	-9.748	4.860	1.00 17.60
ATOM	1833	CD	PRO	237	19.919	-9.211	3.665	1.00 17.60
ATOM	1834	CA	PRO	237	21.200	-11.022	4.536	1.00 17.60
ATOM	1835	CB	PRO	237	20.651	-11.392	3.228	1.00 17.60
ATOM	1836	CG	PRO	237	19.512	-10.475	2.998	1.00 17.60
	1837	C	PRO	237	22.707	-10.963	4.472	1.00 17.60
	1838	O	PRO	237	23.426	-11.959	4.649	1.00 17.60
ATOM	1839	N	PHE	238	23.063	-9.748	4.045	1.00 17.60
ATOM	1840	CA	PHE	238	24.396	-9.244	3.800	1.00 17.60
ATOM	1841	CB	PHE	238	24.788	-8.943	2.331	1.00 17.60
ATOM	1842	CG	PHE	238	24.056	-9.806	1.343	1.00 17.60
ATOM	1843	CD1	PHE	238	22.885	-9.341	0.811	1.00 17.60
ATOM	1844	CD2	PHE	238	24.527	-11.056	1.047	1.00 17.60
ATOM	1845	CE1	PHE	238	22.172	-10.162	-0.032	1.00 17.60
ATOM	1846	CE2	PHE	238	23.809	-11.866	0.206	1.00 17.60
ATOM	1847	CZ	PHE	238	22.630	-11.429	-0.336	1.00 17.60
ATOM	1848	C	PHE	238	24.163	-7.886	4.382	1.00 17.60
ATOM	1849	O	PHE	238	23.065	-7.316	4.145	1.00 17.60
ATOM	1850	N	PHE	239	25.228	-7.500	5.099	1.00 17.60
ATOM	1851	CA	PHE	239	25.462	-6.215	5.740	1.00 17.60
ATOM	1852	CB	PHE	239	24.525	-6.053	6.947	1.00 17.60
ATOM	1853	CG	PHE	239	24.660	-7.010	8.125	1.00 17.60
ATOM	1854	CD1	PHE	239	24.064	-8.253	8.062	1.00 17.60
ATOM	1855	CD2	PHE	239	25.398	-6.622	9.225	1.00 17.60
ATOM	1856	CE1	PHE	239	24.228	-9.107	9.223	1.00 17.60
ATOM	1857	CE2	PHE	239	25.553	-7.489	10.269	1.00 17.60
ATOM	1858	CZ	PHE	239	24.972	-8.735	10.228	1.00 17.60
ATOM	1859	C	PHE	239	26.956	-6.091	6.191	1.00 17.60
ATOM	1860	O	PHE	239	27.628	-7.128	6.209	1.00 17.60
ATOM	1861	N	ALA	240	27.542	-4.889	6.440	1.00 17.60
	1862	CA	ALA	240	28.837	-4.616	7.050	1.00 17.60
	1863	CB	ALA	240	29.957	-4.786	6.125	1.00 17.60
ATOM	1864	C	ALA	240	28.804	-3.127	7.354	1.00 17.60
ATOM	1865	O	ALA	240	27.804	-2.518	6.978	1.00 17.60
ATOM	1866	N	ASP	241	29.697	-2.372	7.992	1.00 17.60
ATOM	1867	CA	ASP	241	29.457	-0.922	8.027	1.00 17.60
ATOM	1868	CB	ASP	241	29.690	-0.330	9.428	1.00 17.60
ATOM	1869	CG	ASP	241	30.505	-1.230	10.345	1.00 17.60
ATOM	1870	OD1	ASP	241	31.687	-1.461	10.058	1.00 17.60
ATOM	1871	OD2	ASP	241	29.966	-1.732	11.340	1.00 17.60
ATOM	1872	C	ASP	241	30.673	-0.415	7.021	1.00 17.60
ATOM	1873	O	ASP	241	31.643	-0.535	7.347	1.00 17.60
ATOM	1874	N	GLN	242	30.121	0.011	5.798	1.00 17.60
ATOM	1875	CA	GLN	242	31.009	0.487	4.714	1.00 17.60
ATOM	1876	CB	GLN	242	32.536	0.171	4.787	1.00 17.60
ATOM	1877	CG	GLN	242	33.588	1.136	5.358	1.00 17.60
ATOM	1878	CD	GLN	242	33.096	2.009	6.520	1.00 17.60
ATOM	1879	OE1	GLN	242	32.386	3.002	6.315	1.00 17.60
ATOM	1880	NE2	GLN	242	33.411	1.676	7.772	1.00 17.60
ATOM	1881	C	GLN	242	30.563	-0.337	3.542	1.00 17.60
ATOM	1882	O	GLN	242	30.838	-1.547	3.494	1.00 17.60

ATOM	1883	N	PRO	243	29.877	0.216	2.559	1.00 17.60
ATOM	1884	CD	PRO	243	29.893	1.599	2.184	1.00 17.60
ATOM	1885	CA	PRO	243	29.078	-0.521	1.600	1.00 17.60
ATOM	1886	CB	PRO	243	28.497	0.532	0.678	1.00 17.60
ATOM	1887	CG	PRO	243	28.536	1.775	1.493	1.00 17.60
ATOM	1888	C	PRO	243	29.910	-1.561	0.869	1.00 17.60
ATOM	1889	O	PRO	243	29.514	-2.678	0.777	1.00 17.60
ATOM	1890	N	ILE	244	31.105	-1.388	0.416	1.00 17.60
ATOM	1891	CA	ILE	244	32.047	-2.051	-0.289	1.00 17.60
ATOM	1892	CB	ILE	244	33.420	-1.276	-0.286	1.00 17.60
ATOM	1893	CG2	ILE	244	34.314	-1.396	0.944	1.00 17.60
ATOM	1894	CG1	ILE	244	34.088	-1.764	-1.511	1.00 17.60
ATOM	1895	CD1	ILE	244	33.694	-0.698	-2.590	1.00 17.60
ATOM	1896	C	ILE	244	32.150	-3.452	0.301	1.00 17.60
ATOM	1897	O	ILE	244	32.083	-4.486	-0.390	1.00 17.60
ATOM	1898	N	GLN	245	32.162	-3.448	1.638	1.00 17.60
ATOM	1899	CA	GLN	245	32.245	-4.681	2.385	1.00 17.60
ATOM	1900	CB	GLN	245	32.369	-4.238	3.821	1.00 17.60
ATOM	1901	CG	GLN	245	33.738	-3.611	4.226	1.00 17.60
ATOM	1902	CD	GLN	245	33.687	-2.825	5.540	1.00 17.60
ATOM	1903	OE1	GLN	245	32.855	-2.992	6.450	1.00 17.60
ATOM	1904	NE2	GLN	245	34.599	-1.866	5.626	1.00 17.60
ATOM	1905	C	GLN	245	31.044	-5.612	2.111	1.00 17.60
ATOM	1906	O	GLN	245	31.164	-6.823	1.815	1.00 17.60
ATOM	1907	N	ILE	246	29.904	-4.978	2.086	1.00 17.60
ATOM	1908	CA	ILE	246	28.662	-5.532	1.751	1.00 17.60
ATOM	1909	CB	ILE	246	27.524	-4.441	1.825	1.00 17.60
ATOM	1910	CG2	ILE	246	26.211	-5.178	1.808	1.00 17.60
ATOM	1911	CG1	ILE	246	27.607	-3.554	3.069	1.00 17.60
ATOM	1912	CD1	ILE	246	26.584	-2.427	3.036	1.00 17.60
ATOM	1913	C	ILE	246	28.752	-6.123	0.320	1.00 17.60
ATOM	1914	O	ILE	246	28.544	-7.318	0.014	1.00 17.60
ATOM	1915	N	TYR	247	29.199	-5.272	-0.591	1.00 17.60
ATOM	1916	CA	TYR	247	29.202	-5.582	-2.014	1.00 17.60
ATOM	1917	CB	TYR	247	29.889	-4.467	-2.736	1.00 17.60
ATOM	1918	CG	TYR	247	29.145	-3.139	-2.729	1.00 17.60
ATOM	1919	CD1	TYR	247	29.809	-2.074	-3.269	1.00 17.60
ATOM	1920	CE1	TYR	247	29.199	-0.847	-3.338	1.00 17.60
ATOM	1921	CD2	TYR	247	27.862	-2.998	-2.230	1.00 17.60
ATOM	1922	CE2	TYR	247	27.235	-1.785	-2.279	1.00 17.60
ATOM	1923	CZ	TYR	247	27.916	-0.728	-2.846	1.00 17.60
ATOM	1924	OH	TYR	247	27.298	0.476	-3.007	1.00 17.60
ATOM	1925	C	TYR	247	29.866	-6.866	-2.308	1.00 17.60
ATOM	1926	O	TYR	247	29.321	-7.721	-2.961	1.00 17.60
ATOM	1927	N	GLU	248	30.959	-7.039	-1.620	1.00 17.60
ATOM	1928	CA	GLU	248	31.782	-8.221	-1.679	1.00 17.60
ATOM	1929	CB	GLU	248	32.844	-8.026	-0.562	1.00 17.60
ATOM	1930	CG	GLU	248	34.007	-9.014	-0.379	1.00 17.60
ATOM	1931	CD	GLU	248	33.591	-10.340	0.283	1.00 17.60
ATOM	1932	OE1	GLU	248	33.919	-11.422	-0.240	1.00 17.60
ATOM	1933	OE2	GLU	248	32.922	-10.290	1.328	1.00 17.60
ATOM	1934	C	GLU	248	30.928	-9.443	-1.494	1.00 17.60
ATOM	1935	O	GLU	248	30.890	-10.306	-2.360	1.00 17.60
ATOM	1936	N	LYS	249	30.157	-9.405	-0.608	1.00 17.60
ATOM	1937	CA	LYS	249	29.321	-10.511	0.040	1.00 17.60
ATOM	1938	CB	LYS	249	28.797	-10.265	1.433	1.00 17.60
ATOM	1939	CG	LYS	249	29.881	-10.314	2.477	1.00 17.60
ATOM	1940	CD	LYS	249	29.981	-9.080	3.367	1.00 17.60
ATOM	1941	CE	LYS	249	28.889	-8.994	4.386	1.00 17.60
ATOM	1942	NZ	LYS	249	28.964	-10.140	5.240	1.00 17.60
ATOM	1943	C	LYS	249	28.134	-10.775	-0.802	1.00 17.60
ATOM	1944	O	LYS	249	27.635	-11.889	-0.901	1.00 17.60
ATOM	1945	N	ILE	250	27.640	-9.645	-1.300	1.00 17.60
ATOM	1946	CA	ILE	250	26.441	-9.590	-2.113	1.00 17.60
ATOM	1947	CB	ILE	250	26.178	-8.092	-2.359	1.00 17.60

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ATOM	1948	CG2	ILE	250	25.909	-7.738	-3.840	1.00	17.60
ATOM	1949	CG1	ILE	250	26.998	-7.718	-1.462	1.00	17.60
ATOM	1950	CD1	ILE	250	23.529	-7.871	-1.968	1.00	17.60
ATOM	1951	C	ILE	250	26.814	-10.405	-3.321	1.00	17.60
ATOM	1952	O	ILE	250	26.155	-11.384	-3.663	1.00	17.60
ATOM	1953	N	VAL	251	27.994	-10.077	-3.835	1.00	17.60
ATOM	1954	CA	VAL	251	28.492	-10.737	-5.003	1.00	17.60
ATOM	1955	CB	VAL	251	29.633	-9.812	-5.416	1.00	17.60
ATOM	1956	CG1	VAL	251	30.539	-10.426	-6.423	1.00	17.60
ATOM	1957	CG2	VAL	251	29.038	-8.669	-6.202	1.00	17.60
ATOM	1958	C	VAL	251	28.033	-12.173	-4.762	1.00	17.60
ATOM	1959	O	VAL	251	28.519	-12.956	-5.651	1.00	17.60
ATOM	1960	N	SER	252	29.389	-12.641	-3.638	1.00	17.60
ATOM	1961	CA	SER	252	29.765	-14.028	-3.492	1.00	17.60
ATOM	1962	CB	SER	252	30.662	-14.234	-2.308	1.00	17.60
ATOM	1963	OG	SER	252	30.253	-13.510	-1.147	1.00	17.60
ATOM	1964	C	SER	252	28.571	-14.881	-3.317	1.00	17.60
ATOM	1965	O	SER	252	28.509	-15.946	-3.916	1.00	17.60
ATOM	1966	N	GLY	253	27.639	-14.472	-2.469	1.00	17.60
ATOM	1967	CA	GLY	253	26.388	-15.217	-2.417	1.00	17.60
ATOM	1968	C	GLY	253	26.565	-16.642	-1.894	1.00	17.60
ATOM	1969	O	GLY	253	26.746	-17.698	-2.502	1.00	17.60
ATOM	1970	N	LYS	254	26.606	-16.541	-0.599	1.00	17.60
ATOM	1971	CA	LYS	254	26.695	-17.657	0.295	1.00	17.60
ATOM	1972	CB	LYS	254	27.782	-17.807	1.041	1.00	17.60
ATOM	1973	CG	LYS	254	28.899	-17.988	0.081	1.00	17.60
ATOM	1974	CD	LYS	254	30.174	-18.339	0.800	1.00	17.60
ATOM	1975	CE	LYS	254	31.293	-18.136	-0.230	1.00	17.60
ATOM	1976	NZ	LYS	254	31.131	-18.921	-1.459	1.00	17.60
ATOM	1977	C	LYS	254	25.433	-16.953	1.142	1.00	17.60
ATOM	1978	O	LYS	254	25.746	-15.818	1.500	1.00	17.60
ATOM	1979	N	VAL	255	24.201	-17.354	1.482	1.00	17.60
ATOM	1980	CA	VAL	255	23.342	-16.510	2.349	1.00	17.60
ATOM	1981	CB	VAL	255	21.833	-16.368	1.896	1.00	17.60
ATOM	1982	CG1	VAL	255	21.370	-15.030	2.470	1.00	17.60
ATOM	1983	CG2	VAL	255	21.603	-16.482	0.380	1.00	17.60
ATOM	1984	C	VAL	255	23.328	-17.306	3.654	1.00	17.60
ATOM	1985	O	VAL	255	23.611	-18.524	3.580	1.00	17.60
ATOM	1986	N	ARG	256	22.972	-16.756	4.844	1.00	17.60
ATOM	1987	CA	ARG	256	22.922	-17.568	6.063	1.00	17.60
ATOM	1988	CB	ARG	256	24.105	-17.151	6.890	1.00	17.60
ATOM	1989	CG	ARG	256	25.219	-18.082	6.447	1.00	17.60
ATOM	1990	CD	ARG	256	24.903	-19.535	6.867	1.00	17.60
ATOM	1991	NE	ARG	256	25.622	-20.115	8.025	1.00	17.60
ATOM	1992	CZ	ARG	256	26.544	-19.551	8.868	1.00	17.60
ATOM	1993	NH1	ARG	256	27.014	-18.263	8.815	1.00	17.60
ATOM	1994	NH2	ARG	256	27.060	-20.395	9.808	1.00	17.60
ATOM	1995	C	ARG	256	21.660	-17.605	6.910	1.00	17.60
ATOM	1996	O	ARG	256	21.452	-16.912	7.898	1.00	17.60
ATOM	1997	N	PHE	257	20.816	-18.510	6.545	1.00	17.60
ATOM	1998	CA	PHE	257	19.555	-18.599	7.179	1.00	17.60
ATOM	1999	CB	PHE	257	18.721	-19.551	6.453	1.00	17.60
ATOM	2000	CG	PHE	257	18.611	-19.193	5.012	1.00	17.60
ATOM	2001	CD1	PHE	257	18.881	-20.144	4.083	1.00	17.60
ATOM	2002	CD2	PHE	257	18.223	-17.939	4.646	1.00	17.60
ATOM	2003	CE1	PHE	257	18.754	-19.847	2.776	1.00	17.60
ATOM	2004	CE2	PHE	257	18.097	-17.634	3.322	1.00	17.60
ATOM	2005	CZ	PHE	257	18.362	-18.596	2.400	1.00	17.60
ATOM	2006	C	PHE	257	19.566	-19.006	8.637	1.00	17.60
ATOM	2007	O	PHE	257	19.996	-20.125	8.994	1.00	17.60
ATOM	2008	N	PRO	258	19.001	-18.123	9.511	1.00	17.60
ATOM	2009	CD	PRO	258	18.688	-16.696	9.235	1.00	17.60
ATOM	2010	CA	PRO	258	18.667	-18.445	10.912	1.00	17.60
ATOM	2011	CB	PRO	258	17.717	-17.320	11.379	1.00	17.60
ATOM	2012	CG	PRO	258	17.509	-16.382	10.200	1.00	17.60
ATOM	2013	C	PRO	258	18.080	-19.817	11.184	1.00	17.60
ATOM	2014	O	PRO	258	17.476	-20.464	10.318	1.00	17.60
ATOM	2015	N	SER	259	18.244	-20.223	12.438	1.00	17.60
ATOM	2016	CA	SER	259	17.652	-21.470	12.911	1.00	17.60
ATOM	2017	CB	SER	259	18.197	-21.803	14.309	1.00	17.60
ATOM	2018	OG	SER	259	18.408	-20.589	15.064	1.00	17.60
ATOM	2019	C	SER	259	16.129	-21.414	12.986	1.00	17.60
ATOM	2020	O	SER	259	15.476	-22.451	12.891	1.00	17.60
ATOM	2021	N	HIS	260	15.524	-20.217	13.135	1.00	17.60
ATOM	2022	CA	HIS	260	14.070	-20.105	13.298	1.00	17.60
ATOM	2023	CB	HIS	260	13.732	-18.943	14.251	1.00	17.60
ATOM	2024	CG	HIS	260	14.351	-17.562	13.811	1.00	17.60
ATOM	2025	CD2	HIS	260	15.447	-17.094	13.752	1.00	17.60
ATOM	2026	ND1	HIS	260	13.362	-16.566	13.455	1.00	17.60
ATOM	2027	CE1	HIS	260	14.109	-15.511	13.189	1.00	17.60
ATOM	2028	NE2	HIS	260	15.371	-15.844	13.373	1.00	17.60
ATOM	2029	C	HIS	260	13.271	-19.916	12.003	1.00	17.60
ATOM	2030	O	HIS	260	12.181	-19.314	12.000	1.00	17.60
ATOM	2031	N	PHE	261	13.836	-20.427	10.901	1.00	17.60
ATOM	2032	CA	PHE	261	13.273	-20.100	9.641	1.00	17.60
ATOM	2033	CB	PHE	261	14.396	-19.827	8.707	1.00	17.60
ATOM	2034	CG	PHE	261	14.538	-18.322	8.566	1.00	17.60
ATOM	2035	CD1	PHE	261	13.971	-17.432	9.495	1.00	17.60
ATOM	2036	CD2	PHE	261	15.254	-17.812	7.488	1.00	17.60
ATOM	2037	CE1	PHE	261	14.127	-16.067	9.347	1.00	17.60
ATOM	2038	CE2	PHE	261	15.403	-16.446	7.349	1.00	17.60
ATOM	2039	CZ	PHE	261	14.842	-15.578	8.275	1.00	17.60
ATOM	2040	C	PHE	261	12.285	-21.005	9.003	1.00	17.60
ATOM	2041	O	PHE	261	11.400	-20.459	8.362	1.00	17.60
ATOM	2042	N	SER	262	12.265	-22.302	9.171	1.00	17.60
ATOM	2043	CA	SER	262	11.352	-23.169	8.427	1.00	17.60
ATOM	2044	CB	SER	262	9.890	-22.682	8.169	1.00	17.60
ATOM	2045	OG	SER	262	9.666	-21.938	6.986	1.00	17.60
ATOM	2046	C	SER	262	11.955	-23.265	7.043	1.00	17.60
ATOM	2047	O	SER	262	12.594	-22.333	6.503	1.00	17.60
ATOM	2048	N	SER	263	11.733	-24.469	6.494	1.00	17.60
ATOM	2049	CA	SER	263	12.283	-24.832	5.191	1.00	17.60
ATOM	2050	CB	SER	263	11.897	-26.302	4.915	1.00	17.60
ATOM	2051	OG	SER	263	12.062	-27.159	6.088	1.00	17.60
ATOM	2052	C	SER	263	11.727	-23.868	4.163	1.00	17.60
ATOM	2053	O	SER	263	12.470	-23.119	3.535	1.00	17.60
ATOM	2054	N	ASP	264	10.411	-23.700	4.267	1.00	17.60
ATOM	2055	CA	ASP	264	9.639	-22.927	3.318	1.00	17.60
ATOM	2056	CB	ASP	264	8.211	-22.772	3.851	1.00	17.60
ATOM	2057	CG	ASP	264	7.203	-23.880	3.522	1.00	17.60
ATOM	2058	OD1	ASP	264	6.083	-23.658	3.977	1.00	17.60
ATOM	2059	OD2	ASP	264	7.482	-24.909	2.857	1.00	17.60
ATOM	2060	C	ASP	264	10.216	-21.573	3.006	1.00	17.60
ATOM	2061	O	ASP	264	10.463	-21.298	1.817	1.00	17.60
ATOM	2062	N	LEU	265	10.477	-20.800	4.065	1.00	17.60
ATOM	2063	CA	LEU	265	11.003	-19.477	3.860	1.00	17.60
ATOM	2064	CB	LEU	265	11.071	-18.608	5.099	1.00	17.60
ATOM	2065	CG	LEU	265	11.562	-17.191	4.814	1.00	17.60
ATOM	2066	CD1	LEU	265	10.632	-16.531	3.829	1.00	17.60
ATOM	2067	CD2	LEU	265	11.649	-16.403	6.091	1.00	17.60
ATOM	2068	C	LEU	265	12.406	-19.632	3.374	1.00	17.60
ATOM	2069	O	LEU	265	12.688	-19.009	2.357	1.00	17.60
ATOM	2070	N	LYS	266	13.225	-20.506	3.944	1.00	17.60
ATOM	2071	CA	LYS	266	14.591	-20.685	3.489	1.00	17.60
ATOM	2072	CB	LYS	266	15.242	-21.871	4.108	1.00	17.60
ATOM	2073	CG	LYS	266	15.626	-21.725	5.535	1.00	17.60
ATOM	2074	CD	LYS	266	16.311	-23.052	5.808	1.00	17.60
ATOM	2075	CE	LYS	266	16.304	-23.317	7.305	1.00	17.60
ATOM	2076	NZ	LYS	266	14.969	-23.329	7.936	1.00	17.60
ATOM	2077	C	LYS	266	14.631	-20.936	2.002	1.00	17.60

ATOM	2078	O	LYS	266	15.661	-20.442	1.241	1.00	17.60
ATOM	2079	N	ASP	267	13.601	-21.654	1.618	1.00	17.60
ATOM	2080	CA	ASP	267	13.439	-22.100	0.296	1.00	17.60
ATOM	2081	CB	ASP	267	12.412	-23.144	0.246	1.00	17.60
ATOM	2082	CG	ASP	267	12.441	-23.703	-1.155	1.00	17.60
ATOM	2083	OD1	ASP	267	13.479	-24.264	-1.538	1.00	17.60
ATOM	2084	OD2	ASP	267	11.453	-23.513	-1.869	1.00	17.60
ATOM	2085	C	ASP	267	13.018	-20.983	-0.607	1.00	17.60
ATOM	2086	O	ASP	267	13.476	-20.936	-1.756	1.00	17.60
ATOM	2087	N	LEU	268	12.135	-20.084	-0.212	1.00	17.60
ATOM	2088	CA	LEU	268	11.825	-19.036	-1.164	1.00	17.60
ATOM	2089	CB	LEU	268	10.565	-18.374	-0.662	1.00	17.60
ATOM	2090	CG	LEU	268	9.929	-17.186	-1.362	1.00	17.60
ATOM	2091	CD1	LEU	268	9.629	-17.367	-2.839	1.00	17.60
ATOM	2092	CD2	LEU	268	8.717	-16.925	-0.465	1.00	17.60
ATOM	2093	C	LEU	268	13.032	-18.092	-1.273	1.00	17.60
ATOM	2094	O	LEU	268	13.415	-17.603	-2.339	1.00	17.60
ATOM	2095	N	LEU	269	13.740	-17.927	-0.174	1.00	17.60
ATOM	2096	CA	LEU	269	14.897	-17.062	-0.147	1.00	17.60
	2097	CB	LEU	269	15.249	-16.867	1.312	1.00	17.60
ATOM	2098	CG	LEU	269	14.508	-15.807	2.099	1.00	17.60
ATOM	2099	CD1	LEU	269	13.094	-15.659	1.679	1.00	17.60
ATOM	2100	CD2	LEU	269	14.562	-16.213	3.540	1.00	17.60
ATOM	2101	C	LEU	269	16.078	-17.569	-0.966	1.00	17.60
ATOM	2102	O	LEU	269	16.692	-16.845	-1.750	1.00	17.60
ATOM	2103	N	ARG	270	16.338	-18.847	-0.879	1.00	17.60
ATOM	2104	CA	ARG	270	17.451	-19.604	-1.586	1.00	17.60
ATOM	2105	CB	ARG	270	17.755	-20.782	-1.029	1.00	17.60
ATOM	2106	CG	ARG	270	16.588	-21.696	-1.282	1.00	17.60
ATOM	2107	CD	ARG	270	16.759	-23.140	-0.894	1.00	17.60
ATOM	2108	NE	ARG	270	16.966	-23.257	0.549	1.00	17.60
ATOM	2109	CZ	ARG	270	17.099	-24.451	1.196	1.00	17.60
ATOM	2110	NH1	ARG	270	17.047	-25.644	0.538	1.00	17.60
ATOM	2111	NH2	ARG	270	17.287	-26.439	2.536	1.00	17.60
ATOM	2112	C	ARG	270	17.082	-19.465	-3.058	1.00	17.60
ATOM	2113	O	ARG	270	17.967	-19.643	-3.890	1.00	17.60
ATOM	2114	N	ASN	271	15.795	-19.377	-3.415	1.00	17.60
ATOM	2115	CA	ASN	271	15.368	-19.268	-4.813	1.00	17.60
ATOM	2116	CB	ASN	271	13.997	-19.901	-5.159	1.00	17.60
ATOM	2117	CG	ASN	271	13.780	-21.617	-5.278	1.00	17.60
ATOM	2118	OD1	ASN	271	12.743	-21.913	-4.807	1.00	17.60
ATOM	2119	ND2	ASN	271	14.614	-22.258	-5.926	1.00	17.60
ATOM	2120	C	ASN	271	15.173	-17.803	-5.208	1.00	17.60
AT	2121	O	ASN	271	14.920	-17.565	-6.389	1.00	17.60
A	2122	N	LEU	272	15.160	-16.770	-4.362	1.00	17.60
AT...	2123	CA	LEU	272	15.026	-15.417	-4.879	1.00	17.60
ATOM	2124	CB	LEU	272	14.030	-14.590	-4.078	1.00	17.60
ATOM	2125	CG	LEU	272	12.524	-14.755	-4.354	1.00	17.60
ATOM	2126	CD1	LEU	272	11.600	-14.164	-3.288	1.00	17.60
ATOM	2127	CD2	LEU	272	12.318	-16.077	-5.697	1.00	17.60
ATOM	2128	C	LEU	272	16.369	-14.767	-4.814	1.00	17.60
ATOM	2129	O	LEU	272	16.756	-14.083	-5.736	1.00	17.60
ATOM	2130	N	LEU	273	17.158	-14.997	-3.789	1.00	17.60
ATOM	2131	CA	LEU	273	18.478	-14.433	-3.662	1.00	17.60
ATOM	2132	CB	LEU	273	18.712	-14.301	-2.191	1.00	17.60
ATOM	2133	CG	LEU	273	18.081	-13.074	-1.609	1.00	17.60
ATOM	2134	CD1	LEU	273	17.660	-13.322	-0.284	1.00	17.60
ATOM	2135	CD2	LEU	273	19.166	-12.083	-1.404	1.00	17.60
ATOM	2136	C	LEU	273	19.486	-15.337	-4.365	1.00	17.60
ATOM	2137	O	LEU	273	20.508	-15.807	-3.843	1.00	17.60
ATOM	2138	N	GLN	274	19.128	-15.468	-5.652	1.00	17.60
ATOM	2139	CA	GLN	274	19.727	-16.398	-6.619	1.00	17.60
ATOM	2140	CB	GLN	274	18.642	-16.958	-7.577	1.00	17.60
ATOM	2141	CG	GLN	274	18.856	-18.439	-8.016	1.00	17.60
ATOM	2142	CD	GLN	274	20.301	-18.797	-8.317	1.00	17.60
ATOM	2143	OE1	GLN	274	20.862	-18.311	-9.296	1.00	17.60
ATOM	2144	NE2	GLN	274	21.058	-19.500	-7.481	1.00	17.60
ATOM	2145	C	GLN	274	20.747	-15.696	-7.421	1.00	17.60
ATOM	2146	O	GLN	274	20.352	-14.512	-7.848	1.00	17.60
ATOM	2147	N	VAL	275	21.973	-16.060	-7.758	1.00	17.60
ATOM	2148	CA	VAL	275	22.941	-15.123	-8.329	1.00	17.60
ATOM	2149	CB	VAL	275	24.315	-15.698	-8.033	1.00	17.60
ATOM	2150	CG1	VAL	275	25.404	-14.783	-8.570	1.00	17.60
ATOM	2151	CG2	VAL	275	24.499	-15.803	-6.540	1.00	17.60
ATOM	2152	C	VAL	275	22.764	-14.832	-9.818	1.00	17.60
ATOM	2153	O	VAL	275	23.037	-13.758	-10.410	1.00	17.60
ATOM	2154	N	ASP	276	22.308	-15.958	-10.354	1.00	17.60
ATOM	2155	CA	ASP	276	22.149	-16.146	-11.764	1.00	17.60
ATOM	2156	CB	ASP	276	22.474	-17.635	-11.990	1.00	17.60
ATOM	2157	CG	ASP	276	22.686	-18.128	-13.434	1.00	17.60
ATOM	2158	OD1	ASP	276	22.649	-19.360	-13.651	1.00	17.60
ATOM	2159	OD2	ASP	276	22.913	-17.260	-14.316	1.00	17.60
ATOM	2160	C	ASP	276	20.771	-15.751	-17.262	1.00	17.60
ATOM	2161	O	ASP	276	19.813	-16.508	-12.101	1.00	17.60
ATOM	2162	N	LEU	277	20.644	-14.624	-12.931	1.00	17.60
ATOM	2163	CA	LEU	277	19.377	-14.232	-13.555	1.00	17.60
ATOM	2164	CB	LEU	277	19.595	-13.082	-14.556	1.00	17.60
ATOM	2165	CG	LEU	277	19.963	-11.735	-13.917	1.00	17.60
ATOM	2166	CD1	LEU	277	19.660	-10.451	-14.766	1.00	17.60
ATOM	2167	CD2	LEU	277	19.057	-11.628	-12.712	1.00	17.60
ATOM	2168	C	LEU	277	18.576	-15.303	-14.270	1.00	17.60
ATOM	2169	O	LEU	277	17.359	-15.665	-14.130	1.00	17.60
ATOM	2170	N	THR	278	19.276	-16.134	-14.987	1.00	17.60
ATOM	2171	CA	THR	278	18.572	-17.243	-15.617	1.00	17.60
ATOM	2172	CB	THR	278	19.663	-17.883	-16.527	1.00	17.60
ATOM	2173	OG1	THR	278	20.167	-16.780	-17.326	1.00	17.60
ATOM	2174	OG2	THR	278	19.095	-19.080	-17.353	1.00	17.60
ATOM	2175	C	THR	278	17.859	-18.249	-14.695	1.00	17.60
ATOM	2176	O	THR	278	16.909	-18.905	-15.117	1.00	17.60
ATOM	2177	N	LYS	279	18.262	-18.427	-13.447	1.00	17.60
ATOM	2178	CA	LYS	279	17.528	-19.292	-12.534	1.00	17.60
ATOM	2179	CB	LYS	279	18.534	-20.258	-12.048	1.00	17.60
ATOM	2180	CG	LYS	279	19.377	-20.905	-13.147	1.00	17.60
ATOM	2181	CD	LYS	279	20.538	-21.679	-12.474	1.00	17.60
ATOM	2182	CE	LYS	279	20.130	-22.739	-11.426	1.00	17.60
ATOM	2183	NZ	LYS	279	21.325	-23.429	-10.933	1.00	17.60
ATOM	2184	C	LYS	279	16.790	-18.583	-11.351	1.00	17.60
ATOM	2185	O	LYS	279	16.134	-19.232	-10.510	1.00	17.60
ATOM	2186	N	ARG	280	16.923	-17.242	-11.253	1.00	17.60
ATOM	2187	CA	ARG	280	16.230	-16.426	-10.266	1.00	17.60
ATOM	2188	CB	ARG	280	16.431	-16.984	-10.571	1.00	17.60
ATOM	2189	CG	ARG	280	16.030	-16.078	-9.408	1.00	17.60
ATOM	2190	CD	ARG	280	16.787	-12.737	-9.345	1.00	17.60
ATOM	2191	NE	ARG	280	18.231	-12.942	-9.196	1.00	17.60
ATOM	2192	CZ	ARG	280	19.112	-11.946	-9.404	1.00	17.60
ATOM	2193	NH1	ARG	280	18.697	-10.723	-9.742	1.00	17.60
ATOM	2194	NH2	ARG	280	20.431	-12.182	-9.353	1.00	17.60
ATOM	2195	C	ARG	280	14.719	-16.649	-10.208	1.00	17.60
ATOM	2196	O	ARG	280	14.064	-16.601	-11.265	1.00	17.60
ATOM	2197	N	PHE	281	14.094	-16.867	-9.040	1.00	17.60
ATOM	2198	CA	PHE	281	12.646	-16.973	-9.000	1.00	17.60
ATOM	2199	CB	PHE	281	12.304	-17.199	-7.650	1.00	17.60
ATOM	2200	CG	PHE	281	11.552	-18.593	-7.423	1.00	17.60
ATOM	2201	CD1	PHE	281	12.056	-19.689	-8.102	1.00	17.60
ATOM	2202	CD2	PHE	281	10.514	-18.743	-6.518	1.00	17.60
ATOM	2203	CE1	PHE	281	11.502	-20.926	-7.866	1.00	17.60
ATOM	2204	CE2	PHE	281	9.965	-19.972	-6.283	1.00	17.60
ATOM	2205	CZ	PHE	281	10.461	-21.054	-6.961	1.00	17.60
ATOM	2206	C	PHE	281	12.114	-15.639	-9.416	1.00	17.60
ATOM	2207	O	PHE	281	12.663	-14.621	-9.038	1.00	17.60

ATOM	2208	N	GLY	282	11.101	-15.577	-10.240	1.00	17.60
ATOM	2209	CA	GLY	282	10.607	-14.291	-10.639	1.00	17.60
ATOM	2210	C	GLY	282	11.221	-13.972	-11.972	1.00	17.60
ATOM	2211	O	GLY	282	10.756	-13.048	-12.640	1.00	17.60
ATOM	2212	N	ASN	283	12.248	-14.665	-12.445	1.00	17.60
ATOM	2213	CA	ASN	283	12.743	-14.346	-13.787	1.00	17.60
ATOM	2214	CB	ASN	283	14.253	-14.225	-13.769	1.00	17.60
ATOM	2215	CG	ASN	283	14.726	-13.157	-14.756	1.00	17.60
ATOM	2216	OD1	ASN	283	15.915	-12.830	-14.738	1.00	17.60
ATOM	2217	ND2	ASN	283	13.961	-12.500	-15.629	1.00	17.60
ATOM	2218	C	ASN	283	12.381	-15.324	-14.908	1.00	17.60
ATOM	2219	O	ASN	283	12.462	-15.015	-16.088	1.00	17.60
ATOM	2220	N	LEU	284	11.932	-16.517	-14.517	1.00	17.60
ATOM	2221	CA	LEU	284	11.718	-17.686	-15.383	1.00	17.60
ATOM	2222	CB	LEU	284	11.626	-18.940	-14.491	1.00	17.60
ATOM	2223	CG	LEU	284	12.476	-18.906	-13.225	1.00	17.60
ATOM	2224	CD1	LEU	284	11.828	-19.839	-12.251	1.00	17.60
ATOM	2225	CD2	LEU	284	13.929	-19.198	-13.510	1.00	17.60
ATOM	2226	C	LEU	284	10.469	-17.549	-16.224	1.00	17.60
ATOM	2227	O	LEU	284	9.615	-16.696	-15.871	1.00	17.60
ATOM	2228	N	LYS	285	10.230	-18.339	-17.305	1.00	17.60
ATOM	2229	CA	LYS	285	8.936	-18.322	-18.055	1.00	17.60
ATOM	2230	CB	LYS	285	8.971	-19.381	-19.222	1.00	17.60
ATOM	2231	CG	LYS	285	10.215	-19.010	-20.105	1.00	17.60
ATOM	2232	CD	LYS	285	10.130	-19.097	-21.638	1.00	17.60
ATOM	2233	CE	LYS	285	11.372	-18.332	-22.220	1.00	17.60
ATOM	2234	NZ	LYS	285	11.437	-18.246	-23.694	1.00	17.60
ATOM	2235	C	LYS	285	7.899	-18.680	-16.999	1.00	17.60
ATOM	2236	O	LYS	285	8.161	-19.657	-16.328	1.00	17.60
ATOM	2237	N	ASP	286	6.873	-17.889	-16.735	1.00	17.60
ATOM	2238	CA	ASP	286	5.818	-17.968	-15.640	1.00	17.60
ATOM	2239	CB	ASP	286	6.043	-19.163	-14.595	1.00	17.60
ATOM	2240	CG	ASP	286	5.773	-20.636	-15.087	1.00	17.60
ATOM	2241	OD1	ASP	286	4.767	-20.877	-15.812	1.00	17.60
ATOM	2242	OD2	ASP	286	6.575	-21.549	-14.746	1.00	17.60
ATOM	2243	C	ASP	286	6.234	-16.620	-14.950	1.00	17.60
ATOM	2244	O	ASP	286	5.837	-15.541	-15.415	1.00	17.60
ATOM	2245	N	GLY	287	7.004	-16.550	-13.886	1.00	17.60
ATOM	2246	CA	GLY	287	7.401	-15.275	-13.364	1.00	17.60
ATOM	2247	C	GLY	287	6.755	-15.095	-12.039	1.00	17.60
ATOM	2248	O	GLY	287	7.018	-15.879	-11.132	1.00	17.60
ATOM	2249	N	VAL	288	5.847	-14.136	-11.946	1.00	17.60
ATOM	2250	CA	VAL	288	5.110	-13.879	-10.718	1.00	17.60
AT	2251	CB	VAL	288	3.978	-12.923	-10.820	1.00	17.60
A	2252	CG1	VAL	288	4.073	-12.101	-9.566	1.00	17.60
ATOM	2253	CG2	VAL	288	3.966	-12.148	-12.093	1.00	17.60
ATOM	2254	C	VAL	288	4.417	-15.140	-10.221	1.00	17.60
ATOM	2255	O	VAL	288	4.450	-15.419	-9.024	1.00	17.60
ATOM	2256	N	ASN	289	3.825	-15.994	-11.059	1.00	17.60
ATOM	2257	CA	ASN	289	3.190	-17.197	-10.541	1.00	17.60
ATOM	2258	CB	ASN	289	2.306	-17.880	-11.598	1.00	17.60
ATOM	2259	CG	ASN	289	1.085	-16.978	-11.756	1.00	17.60
ATOM	2260	OD1	ASN	289	1.126	-16.013	-12.524	1.00	17.60
ATOM	2261	ND2	ASN	289	0.000	-17.132	-10.992	1.00	17.60
ATOM	2262	C	ASN	289	4.174	-18.204	-10.012	1.00	17.60
ATOM	2263	O	ASN	289	3.734	-19.257	-9.588	1.00	17.60
ATOM	2264	N	ASP	290	5.486	-17.972	-9.994	1.00	17.60
ATOM	2265	CA	ASP	290	6.383	-18.905	-9.364	1.00	17.60
ATOM	2266	CB	ASP	290	7.806	-18.805	-9.886	1.00	17.60
ATOM	2267	CG	ASP	290	8.101	-19.139	-11.359	1.00	17.60
ATOM	2268	OD1	ASP	290	8.797	-18.348	-12.028	1.00	17.60
ATOM	2269	OD2	ASP	290	7.687	-20.204	-11.835	1.00	17.60
ATOM	2270	C	ASP	290	6.324	-18.357	-7.955	1.00	17.60
ATOM	2271	O	ASP	290	6.118	-19.151	-7.028	1.00	17.60
ATOM	2272	N	ILE	291	6.402	-17.022	-7.767	1.00	17.60
ATOM	2273	CA	ILE	291	6.474	-16.512	-6.425	1.00	17.60
ATOM	2274	CB	ILE	291	6.661	-14.970	-6.302	1.00	17.60
ATOM	2275	CG2	ILE	291	6.664	-14.635	-4.829	1.00	17.60
ATOM	2276	CG1	ILE	291	8.052	-14.467	-6.604	1.00	17.60
ATOM	2277	CD1	ILE	291	8.564	-14.549	-8.022	1.00	17.60
ATOM	2278	C	ILE	291	5.173	-16.889	-5.783	1.00	17.60
ATOM	2279	O	ILE	291	5.173	-17.600	-4.781	1.00	17.60
ATOM	2280	N	LYS	292	4.067	-16.535	-6.407	1.00	17.60
ATOM	2281	CA	LYS	292	2.714	-16.893	-5.911	1.00	17.60
ATOM	2282	CB	LYS	292	1.584	-16.437	-6.896	1.00	17.60
ATOM	2283	CG	LYS	292	1.458	-14.895	-7.147	1.00	17.60
ATOM	2284	CD	LYS	292	0.355	-14.500	-8.107	1.00	17.60
ATOM	2285	CE	LYS	292	0.312	-13.032	-8.233	1.00	17.60
ATOM	2286	NZ	LYS	292	-0.907	-12.702	-8.936	1.00	17.60
ATOM	2287	C	LYS	292	2.428	-18.376	-5.617	1.00	17.60
ATOM	2288	O	LYS	292	1.648	-18.632	-4.701	1.00	17.60
ATOM	2289	N	ASN	293	3.021	-19.398	-6.228	1.00	17.60
ATOM	2290	CA	ASN	293	2.531	-20.742	-5.980	1.00	17.60
ATOM	2291	CB	ASN	293	2.510	-21.531	-7.291	1.00	17.60
ATOM	2292	CG	ASN	293	1.479	-20.958	-8.248	1.00	17.60
ATOM	2293	OD1	ASN	293	0.486	-20.383	-7.817	1.00	17.60
ATOM	2294	ND2	ASN	293	1.645	-20.944	-9.574	1.00	17.60
ATOM	2295	C	ASN	293	3.425	-21.411	-4.998	1.00	17.60
ATOM	2296	O	ASN	293	3.462	-22.638	-4.822	1.00	17.60
ATOM	2297	N	HIS	294	4.208	-20.597	-4.300	1.00	17.60
ATOM	2298	CA	HIS	294	5.265	-21.176	-3.527	1.00	17.60
ATOM	2299	CB	HIS	294	6.272	-20.255	-3.053	1.00	17.60
ATOM	2300	CG	HIS	294	7.522	-20.993	-2.614	1.00	17.60
ATOM	2301	CD2	HIS	294	8.579	-21.241	-3.477	1.00	17.60
ATOM	2302	ND1	HIS	294	7.909	-21.326	-1.380	1.00	17.60
ATOM	2303	CE1	HIS	294	9.162	-21.724	-1.491	1.00	17.60
ATOM	2304	NE2	HIS	294	9.564	-21.675	-2.745	1.00	17.60
ATOM	2305	C	HIS	294	4.559	-21.590	-2.337	1.00	17.60
ATOM	2306	O	HIS	294	3.815	-20.876	-1.707	1.00	17.60
ATOM	2307	N	LYS	295	5.100	-22.737	-2.049	1.00	17.60
ATOM	2308	CA	LYS	295	4.737	-23.486	-0.880	1.00	17.60
ATOM	2309	CB	LYS	295	5.771	-24.624	-0.775	1.00	17.60
ATOM	2310	CG	LYS	295	6.025	-25.636	-1.991	1.00	17.60
ATOM	2311	CD	LYS	295	6.683	-25.162	-3.393	1.00	17.60
ATOM	2312	CE	LYS	295	8.166	-24.629	-3.600	1.00	17.60
ATOM	2313	NZ	LYS	295	8.662	-24.062	-4.677	1.00	17.60
ATOM	2314	C	LYS	295	4.682	-22.556	0.338	1.00	17.60
ATOM	2315	O	LYS	295	3.745	-22.673	1.107	1.00	17.60
ATOM	2316	N	TRP	296	5.530	-21.520	0.456	1.00	17.60
ATOM	2317	CA	TRP	296	5.439	-20.578	1.581	1.00	17.60
ATOM	2318	CB	TRP	296	6.686	-19.688	1.585	1.00	17.60
ATOM	2319	CG	TRP	296	6.964	-18.846	2.840	1.00	17.60
ATOM	2320	CD2	TRP	296	6.771	-17.488	3.002	1.00	17.60
ATOM	2321	CE2	TRP	296	7.198	-17.290	4.317	1.00	17.60
ATOM	2322	CE3	TRP	296	6.314	-16.431	2.248	1.00	17.60
ATOM	2323	CD1	TRP	296	7.484	-19.413	3.984	1.00	17.60
ATOM	2324	NE1	TRP	296	7.614	-18.450	4.866	1.00	17.60
ATOM	2325	CZ2	TRP	296	7.187	-16.043	4.917	1.00	17.60
ATOM	2326	CZ3	TRP	296	6.307	-15.193	2.850	1.00	17.60
ATOM	2327	CH2	TRP	296	6.737	-14.995	4.163	1.00	17.60
ATOM	2328	C	TRP	296	4.165	-19.701	1.506	1.00	17.60
ATOM	2329	O	TRP	296	3.579	-19.452	2.552	1.00	17.60
ATOM	2330	N	PHE	297	3.657	-19.184	0.394	1.00	17.60
ATOM	2331	CA	PHE	297	2.487	-18.343	0.457	1.00	17.60
ATOM	2332	CB	PHE	297	2.293	-17.272	-0.617	1.00	17.60
ATOM	2333	CG	PHE	297	3.354	-16.198	-0.817	1.00	17.60
ATOM	2334	CD1	PHE	297	3.212	-14.984	-0.219	1.00	17.60
ATOM	2335	CD2	PHE	297	4.447	-16.437	-1.616	1.00	17.60
ATOM	2336	CE1	PHE	297	4.153	-13.998	-0.408	1.00	17.60
ATOM	2337	CE2	PHE	297	5.385	-15.447	-1.798	1.00	17.60

ATOM	2398	CZ	PHE	297	5.244	-14.227	-1.198	1.00	17.60
ATOM	2399	C	PHE	297	1.538	-19.393	0.061	1.00	17.60
ATOM	2400	O	PHE	297	1.583	-19.826	-1.092	1.00	17.60
ATOM	2401	N	ALA	298	0.713	-19.849	0.981	1.00	17.60
ATOM	2402	CA	ALA	298	-0.275	-20.841	0.574	1.00	17.60
ATOM	2403	CB	ALA	298	0.378	-22.228	0.736	1.00	17.60
ATOM	2404	C	ALA	298	-1.622	-20.745	1.320	1.00	17.60
ATOM	2405	O	ALA	298	-2.685	-21.258	0.927	1.00	17.60
ATOM	2406	N	THR	299	-1.529	-20.026	2.424	1.00	17.60
ATOM	2407	CA	THR	299	-2.622	-19.500	3.219	1.00	17.60
ATOM	2408	CB	THR	299	-2.153	-19.417	4.667	1.00	17.60
ATOM	2409	OG1	THR	299	-0.716	-19.680	4.730	1.00	17.60
ATOM	2410	CG2	THR	299	-3.081	-20.284	5.495	1.00	17.60
ATOM	2411	C	THR	299	-2.938	-18.062	2.701	1.00	17.60
ATOM	2412	O	THR	299	-3.738	-17.286	3.304	1.00	17.60
ATOM	2413	N	THR	300	-2.200	-17.633	1.633	1.00	17.60
ATOM	2414	CA	THR	300	-2.331	-16.313	1.070	1.00	17.60
ATOM	2415	CB	THR	300	-0.990	-15.959	0.461	1.00	17.60
ATOM	2416	OG1	THR	300	0.035	-16.067	1.459	1.00	17.60
	2417	CG2	THR	300	-1.017	-14.548	-0.057	1.00	17.60
	2418	C	THR	300	-3.459	-16.304	0.058	1.00	17.60
ATOM	2419	O	THR	300	-3.424	-17.025	-0.923	1.00	17.60
ATOM	2420	N	ASP	301	-4.539	-15.576	0.305	1.00	17.60
ATOM	2421	CA	ASP	301	-5.601	-15.432	-0.649	1.00	17.60
ATOM	2422	CB	ASP	301	-6.947	-15.559	0.055	1.00	17.60
ATOM	2423	CG	ASP	301	-8.171	-15.665	-0.895	1.00	17.60
ATOM	2424	OD1	ASP	301	-9.274	-15.968	-0.385	1.00	17.60
ATOM	2425	OD2	ASP	301	-8.041	-15.398	-2.116	1.00	17.60
ATOM	2426	C	ASP	301	-5.370	-14.030	-1.192	1.00	17.60
ATOM	2427	O	ASP	301	-5.717	-12.941	-0.684	1.00	17.60
ATOM	2428	N	TRP	302	-4.712	-14.165	-2.331	1.00	17.60
ATOM	2429	CA	TRP	302	-4.257	-13.050	-3.081	1.00	17.60
ATOM	2430	CB	TRP	302	-3.649	-13.588	-4.289	1.00	17.60
ATOM	2431	CG	TRP	302	-2.353	-14.329	-4.040	1.00	17.60
ATOM	2432	CD2	TRP	302	-1.097	-13.821	-3.714	1.00	17.60
ATOM	2433	CE2	TRP	302	-0.317	-14.976	-3.721	1.00	17.60
ATOM	2434	CE3	TRP	302	-0.454	-12.649	-3.429	1.00	17.60
ATOM	2435	CD1	TRP	302	-2.356	-15.678	-4.216	1.00	17.60
ATOM	2436	NE1	TRP	302	-1.099	-16.041	-4.013	1.00	17.60
ATOM	2437	CZ2	TRP	302	1.050	-14.961	-3.658	1.00	17.60
ATOM	2438	CZ3	TRP	302	0.900	-12.660	-3.170	1.00	17.60
ATOM	2439	CH2	TRP	302	1.660	-13.769	-3.182	1.00	17.60
ATOM	2440	C	TRP	302	-5.367	-12.097	-3.382	1.00	17.60
ATOM	2441	O	TRP	302	-5.162	-10.909	-3.183	1.00	17.60
/	2442	N	ILE	303	-6.599	-12.471	-3.721	1.00	17.60
A	2443	CA	ILE	303	-7.576	-11.394	-3.977	1.00	17.60
ATOM	2444	CB	ILE	303	-8.794	-11.859	-4.852	1.00	17.60
ATOM	2445	CG2	ILE	303	-8.121	-12.642	-6.004	1.00	17.60
ATOM	2446	CG1	ILE	303	-9.881	-12.679	-4.128	1.00	17.60
ATOM	2447	CD1	ILE	303	-11.163	-13.150	-4.960	1.00	17.60
ATOM	2448	C	ILE	303	-8.100	-10.771	-2.706	1.00	17.60
ATOM	2449	O	ILE	303	-8.383	-9.585	-2.696	1.00	17.60
ATOM	2450	N	ALA	304	-8.336	-11.538	-1.620	1.00	17.60
ATOM	2451	CA	ALA	304	-8.520	-11.002	-0.338	1.00	17.60
ATOM	2452	CB	ALA	304	-8.314	-12.051	0.716	1.00	17.60
ATOM	2453	C	ALA	304	-7.600	-9.809	-0.066	1.00	17.60
ATOM	2454	O	ALA	304	-8.028	-8.655	0.063	1.00	17.60
ATOM	2455	N	ILE	305	-6.298	-10.345	-0.231	1.00	17.60
ATOM	2456	CA	ILE	305	-5.261	-9.350	-0.049	1.00	17.60
ATOM	2457	CB	ILE	305	-3.945	-9.813	-0.249	1.00	17.60
ATOM	2458	CG2	ILE	305	-2.818	-8.960	-0.712	1.00	17.60
ATOM	2459	CG1	ILE	305	-3.624	-10.221	1.319	1.00	17.60
ATOM	2460	CD1	ILE	305	-2.614	-11.325	1.068	1.00	17.60
ATOM	2461	C	ILE	305	-5.462	-7.998	-0.988	1.00	17.60
ATOM	2462	O	ILE	305	-5.606	-6.987	-0.489	1.00	17.60

ATOM	2463	N	TYR	306	-5.549	-8.194	-2.285	1.00	17.60
ATOM	2464	CA	TYR	306	-5.746	-7.125	-3.203	1.00	17.60
ATOM	2465	CB	TYR	306	-5.959	-7.753	-4.565	1.00	17.60
ATOM	2466	CG	TYR	306	-6.361	-6.686	-5.574	1.00	17.60
ATOM	2467	CD1	TYR	306	-7.669	-6.581	-6.040	1.00	17.60
ATOM	2468	CE1	TYR	306	-8.075	-5.493	-6.812	1.00	17.60
ATOM	2469	CD2	TYR	306	-5.427	-5.726	-5.897	1.00	17.60
ATOM	2470	CE2	TYR	306	-5.829	-4.660	-6.662	1.00	17.60
ATOM	2471	CZ	TYR	306	-7.134	-4.532	-7.110	1.00	17.60
ATOM	2472	OH	TYR	306	-7.490	-3.393	-7.821	1.00	17.60
ATOM	2473	C	TYR	306	-6.889	-6.222	-2.785	1.00	17.60
ATOM	2474	O	TYR	306	-6.788	-4.993	-2.811	1.00	17.60
ATOM	2475	N	GLN	307	-7.986	-6.799	-2.301	1.00	17.60
ATOM	2476	CA	GLN	307	-9.195	-6.015	-1.971	1.00	17.60
ATOM	2477	CB	GLN	307	-10.433	-6.917	-1.855	1.00	17.60
ATOM	2478	CG	GLN	307	-11.343	-7.406	-3.146	1.00	17.60
ATOM	2479	CD	GLN	307	-11.813	-8.816	-3.125	1.00	17.60
ATOM	2480	OE1	GLN	307	-12.418	-9.302	-2.132	1.00	17.60
ATOM	2481	NE2	GLN	307	-11.727	-9.563	-4.248	1.00	17.60
ATOM	2482	C	GLN	307	-9.066	-5.261	-0.656	1.00	17.60
ATOM	2483	O	GLN	307	-10.044	-4.709	-0.122	1.00	17.60
ATOM	2484	N	ARG	308	-7.816	-5.279	-0.166	1.00	17.60
ATOM	2485	CA	ARG	308	-7.375	-4.763	1.124	1.00	17.60
ATOM	2486	CB	ARG	308	-7.596	-3.275	1.196	1.00	17.60
ATOM	2487	CG	ARG	308	-6.828	-2.628	0.084	1.00	17.60
ATOM	2488	CD	ARG	308	-7.136	-1.203	0.288	1.00	17.60
ATOM	2489	NE	ARG	308	-6.016	-0.516	0.878	1.00	17.60
ATOM	2490	CZ	ARG	308	-5.972	-0.300	2.183	1.00	17.60
ATOM	2491	NH1	ARG	308	-6.952	-0.752	3.002	1.00	17.60
ATOM	2492	NH2	ARG	308	-5.004	0.524	2.615	1.00	17.60
ATOM	2493	C	ARG	308	-8.278	-5.502	2.045	1.00	17.60
ATOM	2494	O	ARG	308	-8.570	-6.670	1.800	1.00	17.60
ATOM	2495	N	LYS	309	-8.667	-4.856	3.121	1.00	17.60
ATOM	2496	CA	LYS	309	-9.689	-5.356	4.021	1.00	17.60
ATOM	2497	CB	LYS	309	-11.135	-5.108	3.338	1.00	17.60
ATOM	2498	CG	LYS	309	-11.535	-3.759	2.568	1.00	17.60
ATOM	2499	CD	LYS	309	-12.024	-2.688	3.363	1.00	17.60
ATOM	2500	CE	LYS	309	-11.843	-1.024	2.763	1.00	17.60
ATOM	2501	NZ	LYS	309	-12.705	-0.667	1.625	1.00	17.60
ATOM	2502	C	LYS	309	-9.481	-6.846	6.410	1.00	17.60
ATOM	2503	O	LYS	309	-8.782	-7.197	5.383	1.00	17.60
ATOM	2504	N	VAL	310	-9.956	-7.716	3.522	1.00	17.60
ATOM	2505	CA	VAL	310	-10.080	-9.134	3.772	1.00	17.60
ATOM	2506	CB	VAL	310	-10.474	-9.846	2.386	1.00	17.60
ATOM	2507	CG1	VAL	310	-11.106	-11.205	2.768	1.00	17.60
ATOM	2508	CG2	VAL	310	-11.537	-9.078	1.524	1.00	17.60
ATOM	2509	C	VAL	310	-8.859	-9.765	4.443	1.00	17.60
ATOM	2510	O	VAL	310	-9.125	-10.420	5.459	1.00	17.60
ATOM	2511	N	GLU	311	-7.567	-9.645	4.075	1.00	17.60
ATOM	2512	CA	GLU	311	-6.596	-10.263	4.971	1.00	17.60
ATOM	2513	CB	GLU	311	-5.242	-10.629	4.315	1.00	17.60
ATOM	2514	CG	GLU	311	-5.257	-12.036	3.644	1.00	17.60
ATOM	2515	CD	GLU	311	-4.551	-13.285	4.251	1.00	17.60
ATOM	2516	OE1	GLU	311	-4.936	-14.386	3.822	1.00	17.60
ATOM	2517	OE2	GLU	311	-3.611	-13.210	5.086	1.00	17.60
ATOM	2518	C	GLU	311	-6.424	-9.160	5.979	1.00	17.60
ATOM	2519	O	GLU	311	-5.955	-8.053	5.763	1.00	17.60
ATOM	2520	N	ALA	312	-7.056	-9.429	7.091	1.00	17.60
ATOM	2521	CA	ALA	312	-6.953	-8.486	8.165	1.00	17.60
ATOM	2522	CB	ALA	312	-7.929	-8.876	9.278	1.00	17.60
ATOM	2523	C	ALA	312	-5.493	-8.486	8.655	1.00	17.60
ATOM	2524	O	ALA	312	-4.815	-9.515	8.702	1.00	17.60
ATOM	2525	N	PRO	313	-5.008	-7.268	8.779	1.00	17.60
ATOM	2526	CD	PRO	313	-5.764	-6.030	8.556	1.00	17.60
ATOM	2527	CA	PRO	313	-3.676	-6.869	9.148	1.00	17.60

ATOM	2468	CB	PRO	313	-3.645	-5.624	9.398	1.00	17.60
ATOM	2469	CG	PRO	313	-5.116	-5.211	9.622	1.00	17.60
ATOM	2470	C	PRO	313	-3.234	-7.555	10.355	1.00	17.60
ATOM	2471	O	PRO	313	-3.840	-7.521	11.424	1.00	17.60
ATOM	2472	N	PHE	314	-2.070	-8.111	10.111	1.00	17.60
ATOM	2473	CA	PHE	314	-1.459	-8.858	11.163	1.00	17.60
ATOM	2474	CB	PHE	314	-0.682	-9.965	10.438	1.00	17.60
ATOM	2475	CG	PHE	314	-1.746	-10.940	9.825	1.00	17.60
ATOM	2476	CD1	PHE	314	-1.567	-11.481	8.549	1.00	17.60
ATOM	2477	CD2	PHE	314	-2.963	-11.205	10.525	1.00	17.60
ATOM	2478	CE1	PHE	314	-2.585	-12.263	7.995	1.00	17.60
ATOM	2479	CE2	PHE	314	-3.992	-11.977	9.962	1.00	17.60
ATOM	2480	CZ	PHE	314	-3.790	-12.490	8.681	1.00	17.60
ATOM	2481	C	PHE	314	-0.726	-7.741	11.792	1.00	17.60
ATOM	2482	O	PHE	314	0.290	-7.267	11.315	1.00	17.60
ATOM	2483	N	ILE	315	-1.476	-7.265	12.775	1.00	17.60
ATOM	2484	CA	ILE	315	-1.200	-6.168	13.666	1.00	17.60
ATOM	2485	CB	ILE	315	-0.477	-6.673	14.910	1.00	17.60
ATOM	2486	CG2	ILE	315	-0.766	-5.688	16.108	1.00	17.60
	2487	CG1	ILE	315	-1.027	-8.000	15.341	1.00	17.60
	2488	CD1	ILE	315	-0.018	-9.021	14.852	1.00	17.60
ATOM	2489	C	ILE	315	-0.439	-5.106	12.934	1.00	17.60
ATOM	2490	O	ILE	315	-1.108	-4.628	12.030	1.00	17.60
ATOM	2491	N	PRO	316	0.759	-4.541	13.195	1.00	17.60
ATOM	2492	CD	PRO	316	1.780	-4.283	12.185	1.00	17.60
ATOM	2493	CA	PRO	316	0.953	-3.524	14.218	1.00	17.60
ATOM	2494	CB	PRO	316	2.463	-3.333	14.272	1.00	17.60
ATOM	2495	CG	PRO	316	2.816	-3.332	12.812	1.00	17.60
ATOM	2496	C	PRO	316	0.161	-2.328	13.692	1.00	17.60
ATOM	2497	O	PRO	316	0.786	-1.306	13.318	1.00	17.60
ATOM	2498	N	LYS	317	-1.195	-2.497	13.714	1.00	17.60
ATOM	2499	CA	LYS	317	-2.199	-1.611	13.141	1.00	17.60
ATOM	2500	CB	LYS	317	-3.589	-2.209	13.411	1.00	17.60
ATOM	2501	CG	LYS	317	-4.309	-2.788	12.194	1.00	17.60
ATOM	2502	CD	LYS	317	-5.497	-3.739	12.510	1.00	17.60
ATOM	2503	CE	LYS	317	-5.004	-5.115	13.118	1.00	17.60
ATOM	2504	NZ	LYS	317	-5.943	-6.251	13.330	1.00	17.60
ATOM	2505	C	LYS	317	-2.063	-0.255	13.757	1.00	17.60
ATOM	2506	O	LYS	317	-3.024	0.213	14.305	1.00	17.60
ATOM	2507	N	PHE	318	-0.938	0.394	13.563	1.00	17.60
ATOM	2508	CA	PHE	318	-0.480	1.576	14.241	1.00	17.60
ATOM	2509	CB	PHE	318	0.222	2.334	13.098	1.00	17.60
ATOM	2510	CG	PHE	318	-0.833	3.184	12.472	1.00	17.60
ATOM	2511	CD1	PHE	318	-1.983	2.639	11.940	1.00	17.60
A	2512	CD2	PHE	318	-0.798	4.564	12.652	1.00	17.60
A.	2513	CE1	PHE	318	-3.060	3.470	11.650	1.00	17.60
ATOM	2514	CE2	PHE	318	-1.874	5.372	12.349	1.00	17.60
ATOM	2515	CZ	PHE	318	-3.032	4.839	11.849	1.00	17.60
ATOM	2516	C	PHE	318	-1.529	2.398	15.079	1.00	17.60
ATOM	2517	O	PHE	318	-2.671	2.735	14.681	1.00	17.60
ATOM	2518	N	LYS	319	-1.110	2.836	16.269	1.00	17.60
ATOM	2519	CA	LYS	319	-1.990	3.543	17.180	1.00	17.60
ATOM	2520	CB	LYS	319	-1.265	3.695	18.504	1.00	17.60
ATOM	2521	CG	LYS	319	-0.071	4.698	18.531	1.00	17.60
ATOM	2522	CD	LYS	319	1.096	4.268	19.456	1.00	17.60
ATOM	2523	CE	LYS	319	1.457	2.791	19.216	1.00	17.60
ATOM	2524	NZ	LYS	319	1.850	2.572	17.830	1.00	17.60
ATOM	2525	C	LYS	319	-2.514	4.892	16.750	1.00	17.60
ATOM	2526	O	LYS	319	-3.305	5.439	17.405	1.00	17.60
ATOM	2527	N	GLY	320	-2.106	5.417	15.629	1.00	17.60
ATOM	2528	CA	GLY	320	-2.475	6.773	15.256	1.00	17.60
ATOM	2529	C	GLY	320	-3.778	6.923	14.473	1.00	17.60
ATOM	2530	O	GLY	320	-3.818	7.575	13.412	1.00	17.60
ATOM	2531	N	PRO	321	-4.883	6.396	15.031	1.00	17.60
ATOM	2532	CD	PRO	321	-5.317	4.979	14.979	1.00	17.60

ATOM	2533	CA	PRO	321	-5.890	7.269	15.661	1.00	17.60
ATOM	2534	CB	PRO	321	-6.906	6.261	16.340	1.00	17.60
ATOM	2535	CG	PRO	321	-6.309	4.842	16.193	1.00	17.60
ATOM	2536	C	PRO	321	-5.218	8.309	16.585	1.00	17.60
ATOM	2537	O	PRO	321	-4.106	8.163	17.140	1.00	17.60
ATOM	2538	N	GLY	322	-5.837	9.490	16.675	1.00	17.60
ATOM	2539	CA	GLY	322	-5.202	10.583	17.415	1.00	17.60
ATOM	2540	C	GLY	322	-5.061	11.407	16.191	1.00	17.60
ATOM	2541	O	GLY	322	-6.055	11.970	15.689	1.00	17.60
ATOM	2542	N	ASP	323	-3.882	11.210	15.692	1.00	17.60
ATOM	2543	CA	ASP	323	-3.418	11.816	14.316	1.00	17.60
ATOM	2544	CB	ASP	323	-4.033	13.295	14.140	1.00	17.60
ATOM	2545	CG	ASP	323	-4.816	13.808	12.913	1.00	17.60
ATOM	2546	OD1	ASP	323	-4.446	13.515	11.759	1.00	17.60
ATOM	2547	OD2	ASP	323	-5.753	14.592	13.359	1.00	17.60
ATOM	2548	C	ASP	323	-1.836	11.899	14.412	1.00	17.60
ATOM	2549	O	ASP	323	-1.161	11.501	15.407	1.00	17.60
ATOM	2550	N	THR	324	-1.436	12.349	13.205	1.00	17.60
ATOM	2551	CA	THR	324	-0.230	13.086	12.903	1.00	17.60
ATOM	2552	CB	THR	324	-0.750	14.616	12.979	1.00	17.60
ATOM	2553	OG1	THR	324	-1.975	14.756	12.200	1.00	17.60
ATOM	2554	CG2	THR	324	0.221	15.626	12.350	1.00	17.60
ATOM	2555	C	THR	324	1.080	12.836	13.655	1.00	17.60
ATOM	2556	O	THR	324	1.116	12.806	14.892	1.00	17.60
ATOM	2557	N	SER	325	2.202	12.846	12.892	1.00	17.60
ATOM	2558	CA	SER	325	3.552	12.666	13.426	1.00	17.60
ATOM	2559	CB	SER	325	4.023	13.859	14.236	1.00	17.60
ATOM	2560	OG	SER	325	4.010	15.035	13.469	1.00	17.60
ATOM	2561	C	SER	325	3.532	11.445	14.328	1.00	17.60
ATOM	2562	O	SER	325	2.794	10.492	13.982	1.00	17.60
ATOM	2563	N	ASN	326	4.402	11.359	15.357	1.00	17.60
ATOM	2564	CA	ASN	326	4.500	10.269	16.323	1.00	17.60
ATOM	2565	CB	ASN	326	3.378	10.477	17.371	1.00	17.60
ATOM	2566	CG	ASN	326	1.979	9.906	17.233	1.00	17.60
ATOM	2567	OD1	ASN	326	1.119	10.286	16.450	1.00	17.60
ATOM	2568	ND2	ASN	326	1.661	9.005	18.131	1.00	17.60
ATOM	2569	C	ASN	326	4.569	8.826	15.824	1.00	17.60
ATOM	2570	O	ASN	326	4.556	7.889	16.631	1.00	17.60
ATOM	2571	N	PHE	327	4.561	8.573	14.514	1.00	17.60
ATOM	2572	CA	PHE	327	4.910	7.300	13.910	1.00	17.60
ATOM	2573	CB	PHE	327	3.775	6.794	13.133	1.00	17.60
ATOM	2574	CG	PHE	327	2.819	6.144	14.059	1.00	17.60
ATOM	2575	CD1	PHE	327	3.185	5.032	14.738	1.00	17.60
ATOM	2576	CD2	PHE	327	1.565	6.637	14.184	1.00	17.60
ATOM	2577	CE1	PHE	327	2.273	4.396	15.546	1.00	17.60
ATOM	2578	CE2	PHE	327	0.677	5.989	15.002	1.00	17.60
ATOM	2579	CZ	PHE	327	1.014	4.873	15.678	1.00	17.60
ATOM	2580	C	PHE	327	6.088	7.523	12.954	1.00	17.60
ATOM	2581	O	PHE	327	6.736	6.606	12.415	1.00	17.60
ATOM	2582	N	ASP	328	6.236	8.803	12.697	1.00	17.60
ATOM	2583	CA	ASP	328	7.308	9.287	11.796	1.00	17.60
ATOM	2584	CB	ASP	328	6.631	10.208	10.723	1.00	17.60
ATOM	2585	CG	ASP	328	5.795	9.527	9.586	1.00	17.60
ATOM	2586	OD1	ASP	328	6.358	9.002	8.611	1.00	17.60
ATOM	2587	OD2	ASP	328	4.559	9.566	9.629	1.00	17.60
ATOM	2588	C	ASP	328	8.183	9.955	12.915	1.00	17.60
ATOM	2589	O	ASP	328	7.767	10.083	14.110	1.00	17.60
ATOM	2590	N	ASP	329	9.418	10.356	12.526	1.00	17.60
ATOM	2591	CA	ASP	329	10.446	10.915	13.401	1.00	17.60
ATOM	2592	CB	ASP	329	11.750	10.306	12.999	1.00	17.60
ATOM	2593	CG	ASP	329	12.133	8.994	13.669	1.00	17.60
ATOM	2594	OD1	ASP	329	11.573	8.707	14.724	1.00	17.60
ATOM	2595	OD2	ASP	329	13.006	8.300	13.075	1.00	17.60
ATOM	2596	C	ASP	329	10.663	12.427	13.528	1.00	17.60
ATOM	2597	O	ASP	329	9.893	13.259	13.039	1.00	17.60

ATOM	2598	N	TYR	330	11.741	12.786	16.227	1.00	17.60
ATOM	2599	CA	TYR	330	11.972	14.177	16.518	1.00	17.60
ATOM	2600	CB	TYR	330	12.007	14.434	16.123	1.00	17.60
ATOM	2601	CG	TYR	330	10.652	14.121	16.823	1.00	17.60
ATOM	2602	CD1	TYR	330	10.548	13.265	17.905	1.00	17.60
ATOM	2603	CE1	TYR	330	9.308	12.791	18.317	1.00	17.60
ATOM	2604	CD2	TYR	330	9.477	14.521	16.208	1.00	17.60
ATOM	2605	CE2	TYR	330	8.240	14.061	16.606	1.00	17.60
ATOM	2606	CZ	TYR	330	8.146	13.172	17.648	1.00	17.60
ATOM	2607	OH	TYR	330	6.893	12.546	17.871	1.00	17.60
ATOM	2608	C	TYR	330	13.292	14.453	13.815	1.00	17.60
ATOM	2609	O	TYR	330	14.370	13.877	14.058	1.00	17.60
ATOM	2610	N	GLU	331	13.100	15.282	12.800	1.00	17.60
ATOM	2611	CA	GLU	331	14.197	15.640	11.929	1.00	17.60
ATOM	2612	CB	GLU	331	13.690	15.335	10.505	1.00	17.60
ATOM	2613	CG	GLU	331	12.859	14.063	10.306	1.00	17.60
ATOM	2614	CD	GLU	331	13.618	12.743	10.158	1.00	17.60
ATOM	2615	OE1	GLU	331	13.079	11.718	9.759	1.00	17.60
[illegible]	2616	OE2	GLU	331	14.796	12.714	10.431	1.00	17.60
	2617	C	GLU	331	14.529	17.126	12.207	1.00	17.60
[illegible]	2618	O	GLU	331	13.720	17.846	12.806	1.00	17.60
ATOM	2619	N	GLU	332	15.685	17.699	11.873	1.00	17.60
ATOM	2620	CA	GLU	332	15.893	19.140	12.046	1.00	17.60
ATOM	2621	CB	GLU	332	17.306	19.601	11.616	1.00	17.60
ATOM	2622	CG	GLU	332	17.689	19.441	10.133	1.00	17.60
ATOM	2623	CD	GLU	332	19.156	19.002	9.740	1.00	17.60
ATOM	2624	OE1	GLU	332	19.314	18.418	8.620	1.00	17.60
ATOM	2625	OE2	GLU	332	20.122	19.243	10.536	1.00	17.60
ATOM	2626	C	GLU	332	14.883	19.832	11.137	1.00	17.60
ATOM	2627	O	GLU	332	14.435	19.231	10.139	1.00	17.60
ATOM	2628	N	GLU	333	14.685	21.058	11.460	1.00	17.60
ATOM	2629	CA	GLU	333	13.579	21.717	10.572	1.00	17.60
ATOM	2630	CB	GLU	333	12.430	22.290	11.356	1.00	17.60
ATOM	2631	CG	GLU	333	11.310	21.527	10.672	1.00	17.60
ATOM	2632	CD	GLU	333	10.155	21.049	11.533	1.00	17.60
ATOM	2633	OE1	GLU	333	10.317	19.866	11.940	1.00	17.60
ATOM	2634	OE2	GLU	333	9.287	21.899	11.754	1.00	17.60
ATOM	2635	C	GLU	333	14.437	22.761	9.924	1.00	17.60
ATOM	2636	O	GLU	333	15.286	23.426	10.554	1.00	17.60
ATOM	2637	N	GLU	334	14.197	22.855	8.626	1.00	17.60
ATOM	2638	CA	GLU	334	15.012	23.686	7.747	1.00	17.60
ATOM	2639	CB	GLU	334	15.896	22.635	6.922	1.00	17.60
ATOM	2640	CG	GLU	334	15.374	21.289	6.242	1.00	17.60
A[illegible]	2641	CD	GLU	334	15.037	20.011	7.088	1.00	17.60
[illegible]	2642	OE1	GLU	334	15.848	19.058	7.193	1.00	17.60
A[illegible]	2643	OE2	GLU	334	13.919	19.952	7.633	1.00	17.60
ATOM	2644	C	GLU	334	14.080	24.619	6.932	1.00	17.60
ATOM	2645	O	GLU	334	12.859	24.453	7.154	1.00	17.60
ATOM	2646	N	ILE	335	14.403	25.596	6.042	1.00	17.60
ATOM	2647	CA	ILE	335	13.286	26.267	5.393	1.00	17.60
ATOM	2648	CB	ILE	335	13.236	27.628	6.014	1.00	17.60
ATOM	2649	CG2	ILE	335	14.160	28.638	5.269	1.00	17.60
ATOM	2650	CG1	ILE	335	11.741	27.994	6.063	1.00	17.60
ATOM	2651	CD1	ILE	335	11.276	29.183	7.003	1.00	17.60
ATOM	2652	C	ILE	335	13.150	26.344	3.867	1.00	17.60
ATOM	2653	O	ILE	335	14.132	26.260	3.116	1.00	17.60
ATOM	2654	N	ARG	336	11.900	26.462	3.372	1.00	17.60
ATOM	2655	CA	ARG	336	11.648	26.564	1.950	1.00	17.60
ATOM	2656	CB	ARG	336	10.204	26.331	1.558	1.00	17.60
ATOM	2657	CG	ARG	336	9.537	25.012	1.896	1.00	17.60
ATOM	2658	CD	ARG	336	8.013	25.104	1.463	1.00	17.60
ATOM	2659	NE	ARG	336	6.930	25.461	2.418	1.00	17.60
ATOM	2660	CZ	ARG	336	6.385	26.701	2.540	1.00	17.60
ATOM	2661	NH1	ARG	336	6.771	27.796	1.837	1.00	17.60
ATOM	2662	NH2	ARG	336	5.294	26.820	3.299	1.00	17.60

ATOM	2663	C	ARG	336	11.953	27.996	1.562	1.00	17.60
ATOM	2664	O	ARG	336	11.432	28.983	2.101	1.00	17.60
ATOM	2665	N	VAL	337	12.829	28.114	0.594	1.00	17.60
ATOM	2666	CA	VAL	337	13.143	29.386	0.013	1.00	17.60
ATOM	2667	CB	VAL	337	14.587	29.705	0.264	1.00	17.60
ATOM	2668	CG1	VAL	337	14.587	30.548	1.573	1.00	17.60
ATOM	2669	CG2	VAL	337	15.463	28.426	0.258	1.00	17.60
ATOM	2670	C	VAL	337	12.027	29.163	-1.442	1.00	17.60
ATOM	2671	O	VAL	337	12.732	28.025	-1.899	1.00	17.60
ATOM	2672	N	SEP	338	12.445	30.308	-2.099	1.00	17.60
ATOM	2673	CA	SEP	338	12.057	30.561	-3.426	1.00	17.60
ATOM	2674	CB	SEP	338	10.530	30.851	-3.269	1.00	17.60
ATOM	2675	OG	SEP	338	9.893	30.555	-1.935	1.00	17.60
ATOM	2676	PD	SEP	338	9.414	31.632	-0.552	1.00	17.60
ATOM	2677	OE1	SEP	338	9.167	33.005	-1.179	1.00	17.60
ATOM	2678	OE2	SEP	338	8.283	30.945	0.230	1.00	17.60
ATOM	2679	OE3	SEP	338	10.699	31.796	0.585	1.00	17.60
ATOM	2680	C	SEP	338	12.826	31.854	-3.756	1.00	17.60
ATOM	2681	O	SEP	338	12.917	32.652	-2.786	1.00	17.60
ATOM	2682	N	ILE	339	13.373	32.352	-4.970	1.00	17.60
ATOM	2683	CA	ILE	339	14.202	33.355	-5.306	1.00	17.60
ATOM	2684	CB	ILE	339	15.741	32.948	-5.161	1.00	17.60
ATOM	2685	CG2	ILE	339	15.937	31.737	-6.038	1.00	17.60
ATOM	2686	CG1	ILE	339	16.759	34.049	-5.553	1.00	17.60
ATOM	2687	CD1	ILE	339	18.279	33.710	-5.501	1.00	17.60
ATOM	2688	C	ILE	339	13.801	33.716	-6.744	1.00	17.60
ATOM	2689	O	ILE	339	12.614	33.493	-6.999	1.00	17.60
ATOM	2690	N	ASN	340	14.580	34.282	-7.718	1.00	17.60
ATOM	2691	CA	ASN	340	14.272	34.311	-9.159	1.00	17.60
ATOM	2692	CB	ASN	340	14.027	35.559	-9.881	1.00	17.60
ATOM	2693	CG	ASN	340	14.420	35.937	-11.356	1.00	17.60
ATOM	2694	OD1	ASN	340	14.068	35.075	-12.170	1.00	17.60
ATOM	2695	ND2	ASN	340	14.489	37.182	-11.902	1.00	17.60
ATOM	2696	C	ASN	340	14.619	32.955	-9.796	1.00	17.60
ATOM	2697	O	ASN	340	14.791	31.981	-9.063	1.00	17.60
ATOM	2698	N	GLU	341	14.887	32.702	-11.069	1.00	17.60
ATOM	2699	CA	GLU	341	15.082	31.351	-11.568	1.00	17.60
ATOM	2700	CB	GLU	341	14.383	31.317	-12.888	1.00	17.60
ATOM	2701	CG	GLU	341	13.819	29.935	-12.990	1.00	17.60
ATOM	2702	CD	GLU	341	12.618	29.889	-13.913	1.00	17.60
ATOM	2703	OE1	GLU	341	11.542	29.693	-13.339	1.00	17.60
ATOM	2704	OE2	GLU	341	12.743	30.049	-15.146	1.00	17.60
ATOM	2705	C	GLU	341	16.403	30.601	-11.691	1.00	17.60
ATOM	2706	O	GLU	341	17.354	30.982	-12.352	1.00	17.60
ATOM	2707	N	LYS	342	16.254	29.434	-11.068	1.00	17.60
ATOM	2708	CA	LYS	342	17.327	28.514	-10.964	1.00	17.60
ATOM	2709	CB	LYS	342	17.230	27.811	-9.614	1.00	17.60
ATOM	2710	CG	LYS	342	18.263	26.542	-8.749	1.00	17.60
ATOM	2711	CD	LYS	342	17.915	30.020	-8.436	1.00	17.60
ATOM	2712	CE	LYS	342	19.109	30.900	-7.996	1.00	17.60
ATOM	2713	NZ	LYS	342	20.120	31.192	-9.034	1.00	17.60
ATOM	2714	C	LYS	342	17.486	27.697	-12.035	1.00	17.60
ATOM	2715	O	LYS	342	18.409	27.705	-12.830	1.00	17.60
ATOM	2716	N	CSH	343	16.768	26.392	-12.227	1.00	17.60
ATOM	2717	CA	CSH	343	17.137	25.671	-13.427	1.00	17.60
ATOM	2718	CB	CSH	343	17.798	24.331	-13.102	1.00	17.60
ATOM	2719	SG	CSH	343	18.799	24.279	-11.615	1.00	17.60
ATOM	2720	C	CSH	343	15.920	25.450	-14.297	1.00	17.60
ATOM	2721	O	CSH	343	15.382	24.331	-14.396	1.00	17.60
ATOM	2722	N	GLY	344	15.567	26.486	-15.078	1.00	17.60
ATOM	2723	CA	GLY	344	14.384	26.421	-15.932	1.00	17.60
ATOM	2724	C	GLY	344	14.376	25.332	-17.001	1.00	17.60
ATOM	2725	O	GLY	344	13.503	24.458	-16.990	1.00	17.60
ATOM	2726	N	LYS	345	15.384	25.342	-17.895	1.00	17.60
ATOM	2727	CA	LYS	345	15.378	24.432	-19.053	1.00	17.60

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ATOM   2778  CB  LYS  345      16.550  24.757 -20.001  1.00 17.60
ATOM   2779  CG  LYS  345      16.439  26.169 -20.707  1.00 17.60
ATOM   2780  CD  LYS  345      15.141  26.300 -21.605  1.00 17.60
ATOM   2781  CE  LYS  345      14.781  27.680 -22.296  1.00 17.60
ATOM   2782  NZ  LYS  345      15.570  28.070 -23.478  1.00 17.60
ATOM   2783  C   LYS  345      15.444  22.975 -18.680  1.00 17.60
ATOM   2784  O   LYS  345      14.965  22.116 -19.386  1.00 17.60
ATOM   2785  N   GLU  346      15.951  22.728 -17.494  1.00 17.60
ATOM   2786  CA  GLU  346      16.142  21.386 -16.968  1.00 17.60
ATOM   2787  CB  GLU  346      17.187  21.506 -15.888  1.00 17.60
ATOM   2788  CG  GLU  346      18.431  22.078 -16.553  1.00 17.60
ATOM   2789  CD  GLU  346      18.900  23.495 -16.229  1.00 17.60
ATOM   2790  OE1 GLU  346      20.007  23.585 -15.707  1.00 17.60
ATOM   2791  OE2 GLU  346      18.223  24.482 -16.529  1.00 17.60
ATOM   2792  C   GLU  346      14.866  20.698 -16.446  1.00 17.60
ATOM   2793  O   GLU  346      14.562  19.536 -16.800  1.00 17.60
ATOM   2794  N   PHE  347      14.328  21.484 -15.632  1.00 17.60
ATOM   2795  CA  PHE  347      12.931  21.043 -14.949  1.00 17.60
ATOM   2796  CB  PHE  347      13.069  21.421 -13.529  1.00 17.60
ATOM   2797  CG  PHE  347      14.260  20.778 -12.950  1.00 17.60
ATOM   2798  CD1 PHE  347      15.401  21.513 -12.844  1.00 17.60
ATOM   2799  CD2 PHE  347      14.208  19.466 -12.588  1.00 17.60
ATOM   2800  CE1 PHE  347      16.544  20.913 -12.371  1.00 17.60
ATOM   2801  CE2 PHE  347      15.355  18.893 -12.118  1.00 17.60
ATOM   2802  CZ  PHE  347      16.521  19.606 -12.012  1.00 17.60
ATOM   2803  C   PHE  347      11.677  21.654 -15.524  1.00 17.60
ATOM   2804  O   PHE  347      10.775  22.080 -14.811  1.00 17.60
ATOM   2805  N   THR  348      11.633  21.689 -16.849  1.00 17.60
ATOM   2806  CA  THR  348      10.522  22.291 -17.565  1.00 17.60
ATOM   2807  CB  THR  348      10.920  22.743 -18.977  1.00 17.60
ATOM   2808  OG1 THR  348      11.925  21.889 -19.494  1.00 17.60
ATOM   2809  CG2 THR  348      11.285  24.205 -18.945  1.00 17.60
ATOM   2810  C   THR  348       9.269  21.458 -17.680  1.00 17.60
ATOM   2811  O   THR  348       8.185  22.040 -17.741  1.00 17.60
ATOM   2812  N   GLU  349       9.349  20.142 -17.730  1.00 17.60
ATOM   2813  CA  GLU  349       8.188  19.301 -17.962  1.00 17.60
ATOM   2814  CB  GLU  349       8.747  18.203 -18.829  1.00 17.60
ATOM   2815  CG  GLU  349       7.851  17.034 -19.108  1.00 17.60
ATOM   2816  CD  GLU  349       8.581  15.690 -19.016  1.00 17.60
ATOM   2817  OE1 GLU  349       9.316  15.355 -19.964  1.00 17.60
ATOM   2818  OE2 GLU  349       8.412  14.981 -17.997  1.00 17.60
ATOM   2819  C   GLU  349       7.629  18.855 -16.604  1.00 17.60
ATOM   2820  O   GLU  349       7.462  17.668 -16.330  1.00 17.60
ATOM   2821  N   PHE  350       7.354  19.766 -15.704  1.00 17.60
ATOM   2822  CA  PHE  350       6.982  19.393 -14.376  1.00 17.60
ATOM   2823  CB  PHE  350       8.291  19.497 -13.503  1.00 17.60
ATOM   2824  CG  PHE  350       8.275  18.888 -12.078  1.00 17.60
ATOM   2825  CD1 PHE  350       7.306  19.222 -11.144  1.00 17.60
ATOM   2826  CD2 PHE  350       9.206  17.930 -11.758  1.00 17.60
ATOM   2827  CE1 PHE  350       7.253  18.606  -9.914  1.00 17.60
ATOM   2828  CE2 PHE  350       9.149  17.315 -10.527  1.00 17.60
ATOM   2829  CZ  PHE  350       8.179  17.664  -9.609  1.00 17.60
ATOM   2830  C   PHE  350       5.877  20.337 -13.926  1.00 17.60
ATOM   2831  O   PHE  350       5.936  21.507 -14.301  1.00 17.60
ATOM   2832  OXT PHE  350       5.019  19.939 -13.118  1.00 17.60
TER
ATOM   2833  N   THR  351      26.441 -13.459  17.857  1.00 17.60
ATOM   2834  CA  THR  351      25.021 -13.729  17.829  1.00 17.60
ATOM   2835  CB  PHE  351      24.486 -13.256  19.195  1.00 17.60
ATOM   2836  CG1 PHE  351      23.449 -12.380  18.814  1.00 17.60
ATOM   2837  CG2 PHE  351      25.504 -12.532  20.177  1.00 17.60
ATOM   2838  C   PHE  351      24.785 -12.806  16.655  1.00 17.60
ATOM   2839  O   PHE  351      25.320 -11.641  16.867  1.00 17.60
ATOM   2840  N   THR  352      24.295 -13.134  15.672  1.00 17.60
ATOM   2841  CA  THR  352      24.364 -12.206  14.339  1.00 17.60
ATOM   2842  CB  THR  352      23.791 -12.917  13.103  1.00 17.60
ATOM   2843  OG1 THR  352      24.247 -14.257  13.192  1.00 17.60
ATOM   2844  CG2 THR  352      24.293 -12.265  11.787  1.00 17.60
ATOM   2845  C   THR  352      23.664 -10.863  14.572  1.00 17.60
ATOM   2846  O   THR  352      24.125  -9.768  14.206  1.00 17.60
ATOM   2847  N   TYR  353      22.575 -10.972  15.330  1.00 17.60
ATOM   2848  CA  TYR  353      21.774  -9.830  15.710  1.00 17.60
ATOM   2849  CB  TYR  353      20.659 -10.292  16.639  1.00 17.60
ATOM   2850  CG  TYR  353      19.481  -9.352  16.580  1.00 17.60
ATOM   2851  CD1 TYR  353      19.488  -8.180  17.295  1.00 17.60
ATOM   2852  CE1 TYR  353      18.465  -7.293  17.099  1.00 17.60
ATOM   2853  CD2 TYR  353      18.440  -9.650  15.711  1.00 17.60
ATOM   2854  CE2 TYR  353      17.381  -8.779  15.515  1.00 17.60
ATOM   2855  CZ  TYR  353      17.400  -7.589  16.211  1.00 17.60
ATOM   2856  OH  TYR  353      16.387  -6.644  15.997  1.00 17.60
ATOM   2857  C   TYR  353      22.722  -8.902  16.436  1.00 17.60
ATOM   2858  O   TYR  353      22.879  -7.788  15.960  1.00 17.60
ATOM   2859  N   ALA  354      23.427  -9.386  17.478  1.00 17.60
ATOM   2860  CA  ALA  354      24.381  -8.602  18.240  1.00 17.60
ATOM   2861  CB  ALA  354      25.168  -9.399  19.238  1.00 17.60
ATOM   2862  C   ALA  354      25.416  -8.040  17.325  1.00 17.60
ATOM   2863  O   ALA  354      25.914  -6.930  17.654  1.00 17.60
ATOM   2864  N   ASP  355      25.786  -8.662  16.195  1.00 17.60
ATOM   2865  CA  ASP  355      26.756  -8.021  15.301  1.00 17.60
ATOM   2866  CB  ASP  355      27.351  -9.029  14.329  1.00 17.60
ATOM   2867  CG  ASP  355      28.176 -10.069  15.076  1.00 17.60
ATOM   2868  OD1 ASP  355      29.318  -9.815  15.673  1.00 17.60
ATOM   2869  OD2 ASP  355      27.653 -11.161  15.282  1.00 17.60
ATOM   2870  C   ASP  355      26.156  -6.866  14.515  1.00 17.60
ATOM   2871  O   ASP  355      26.765  -5.790  14.356  1.00 17.60
ATOM   2872  N   PHE  356      24.928  -7.038  14.072  1.00 17.60
ATOM   2873  CA  PHE  356      24.275  -5.971  13.364  1.00 17.60
ATOM   2874  CB  PHE  356      22.947  -6.491  12.844  1.00 17.60
ATOM   2875  CG  PHE  356      22.159  -5.551  11.966  1.00 17.60
ATOM   2876  CD1 PHE  356      22.718  -5.033  10.815  1.00 17.60
ATOM   2877  CD2 PHE  356      20.879  -5.246  12.306  1.00 17.60
ATOM   2878  CE1 PHE  356      22.014  -4.200   9.981  1.00 17.60
ATOM   2879  CE2 PHE  356      20.182  -4.415  11.472  1.00 17.60
ATOM   2880  CZ  PHE  356      20.740  -3.890  10.318  1.00 17.60
ATOM   2881  C   PHE  356      24.079  -4.758  14.274  1.00 17.60
ATOM   2882  O   PHE  356      24.411  -3.666  13.822  1.00 17.60
ATOM   2883  N   ILE  357      23.645  -4.963  15.553  1.00 17.60
ATOM   2884  CA  ILE  357      23.277  -3.695  16.366  1.00 17.60
ATOM   2885  CB  ILE  357      22.452  -4.092  17.593  1.00 17.60
ATOM   2886  CG2 ILE  357      21.124  -4.485  17.047  1.00 17.60
ATOM   2887  CG1 ILE  357      22.954  -5.265  18.382  1.00 17.60
ATOM   2888  CD1 ILE  357      24.120  -5.106  19.429  1.00 17.60
ATOM   2889  C   ILE  357      24.362  -2.800  16.852  1.00 17.60
ATOM   2890  O   ILE  357      24.145  -1.714  17.374  1.00 17.60
ATOM   2891  N   ALA  358      25.527  -3.387  16.658  1.00 17.60
ATOM   2892  CA  ALA  358      26.812  -2.773  16.874  1.00 17.60
ATOM   2893  CB  ALA  358      27.706  -3.880  17.370  1.00 17.60
ATOM   2894  C   ALA  358      27.370  -2.116  15.569  1.00 17.60
ATOM   2895  O   ALA  358      28.382  -1.398  15.623  1.00 17.60
ATOM   2896  N   SER  359      26.707  -2.248  14.366  1.00 17.60
ATOM   2897  CA  SER  359      27.387  -1.679  13.177  1.00 17.60
ATOM   2898  CB  SER  359      27.198  -2.614  12.062  1.00 17.60
ATOM   2899  OG  SER  359      25.855  -2.979  11.925  1.00 17.60
ATOM   2900  C   SER  359      26.536  -0.461  12.895  1.00 17.60
ATOM   2901  O   SER  359      25.464  -0.262  13.462  1.00 17.60
ATOM   2902  N   GLY  360      27.052   0.286  11.918  1.00 17.60
ATOM   2903  CA  GLY  360      26.663   1.519  11.458  1.00 17.60
ATOM   2904  C   GLY  360      25.270   1.300  10.553  1.00 17.60
ATOM   2905  O   GLY  360      24.670   2.221  10.439  1.00 17.60
ATOM   2906  N   ARG  361      24.983   0.151   9.936  1.00 17.60
```

ATOM	2857	CA	ARG	361	23.826	0.011	9.036	1.00	17.60
ATOM	2858	CB	ARG	361	23.953	-1.239	8.319	1.00	17.60
ATOM	2859	CG	ARG	361	25.149	-1.350	7.129	1.00	17.60
ATOM	2860	CD	ARG	361	25.582	-0.180	6.169	1.00	17.60
ATOM	2861	NE	ARG	361	24.559	0.237	5.204	1.00	17.60
ATOM	2862	CZ	ARG	361	24.592	1.425	4.612	1.00	17.60
ATOM	2863	NH1	ARG	361	25.602	2.259	4.899	1.00	17.60
ATOM	2864	NH2	ARG	361	23.589	1.799	3.796	1.00	17.60
ATOM	2865	C	ARG	361	22.467	-0.095	9.718	1.00	17.60
ATOM	2866	O	ARG	361	21.518	-0.584	9.092	1.00	17.60
ATOM	2867	N	THR	362	22.365	0.282	11.002	1.00	17.60
ATOM	2868	CA	THR	362	21.116	0.199	11.746	1.00	17.60
ATOM	2869	CB	THR	362	21.414	0.053	13.275	1.00	17.60
ATOM	2870	OG1	THR	362	22.348	1.035	13.731	1.00	17.60
ATOM	2871	CG2	THR	362	21.947	-1.349	13.524	1.00	17.60
ATOM	2872	C	THR	362	20.275	1.427	11.468	1.00	17.60
ATOM	2873	O	THR	362	19.060	1.468	11.657	1.00	17.60
ATOM	2874	N	GLY	363	21.009	2.457	11.006	1.00	17.60
ATOM	2875	CA	GLY	363	20.449	3.747	10.657	1.00	17.60
ATOM	2876	C	GLY	363	19.450	3.604	9.510	1.00	17.60
ATOM	2877	O	GLY	363	19.183	2.508	9.028	1.00	17.60
ATOM	2878	N	ARG	364	18.804	4.685	9.073	1.00	17.60
ATOM	2879	CA	ARG	364	17.987	4.653	7.892	1.00	17.60
ATOM	2880	CB	ARG	364	17.061	5.838	7.867	1.00	17.60
ATOM	2881	CG	ARG	364	15.858	5.375	8.638	1.00	17.60
ATOM	2882	CD	ARG	364	14.635	6.271	8.675	1.00	17.60
ATOM	2883	NE	ARG	364	14.157	6.592	7.337	1.00	17.60
ATOM	2884	CZ	ARG	364	14.099	7.870	6.949	1.00	17.60
ATOM	2885	NH1	ARG	364	14.464	8.860	7.811	1.00	17.60
ATOM	2886	NH2	ARG	364	13.793	8.187	5.684	1.00	17.60
ATOM	2887	C	ARG	364	19.075	4.752	6.855	1.00	17.60
ATOM	2888	O	ARG	364	19.910	5.658	6.856	1.00	17.60
ATOM	2889	N	ARG	365	19.152	3.717	6.052	1.00	17.60
ATOM	2890	CA	ARG	365	20.194	3.586	5.075	1.00	17.60
ATOM	2891	CB	ARG	365	20.235	2.128	4.747	1.00	17.60
ATOM	2892	CG	ARG	365	20.533	1.412	5.999	1.00	17.60
ATOM	2893	CD	ARG	365	20.355	-0.009	5.766	1.00	17.60
ATOM	2894	NE	ARG	365	19.066	-0.376	5.249	1.00	17.60
ATOM	2895	CZ	ARG	365	18.127	-0.945	5.981	1.00	17.60
ATOM	2896	NH1	ARG	365	16.974	-1.283	5.440	1.00	17.60
ATOM	2897	NH2	ARG	365	18.275	-1.111	7.290	1.00	17.60
ATOM	2898	C	ARG	365	19.889	4.509	3.887	1.00	17.60
ATOM	2899	O	ARG	365	18.788	4.551	3.299	1.00	17.60
ATOM	2900	N	ASN	366	20.847	5.361	3.549	1.00	17.60
ATOM	2901	CA	ASN	366	20.621	6.231	2.453	1.00	17.60
ATOM	2902	CB	ASN	366	21.567	7.284	2.628	1.00	17.60
ATOM	2903	CG	ASN	366	20.706	8.492	2.470	1.00	17.60
ATOM	2904	OD1	ASN	366	20.544	9.037	1.342	1.00	17.60
ATOM	2905	ND2	ASN	366	20.087	8.840	3.616	1.00	17.60
ATOM	2906	C	ASN	366	20.762	5.546	1.139	1.00	17.60
ATOM	2907	O	ASN	366	21.353	4.461	1.089	1.00	17.60
ATOM	2908	N	ALA	367	20.271	6.203	0.080	1.00	17.60
ATOM	2909	CA	ALA	367	20.282	5.676	-1.294	1.00	17.60
ATOM	2910	CB	ALA	367	19.127	6.172	-2.170	1.00	17.60
ATOM	2911	C	ALA	367	21.517	6.095	-2.034	1.00	17.60
ATOM	2912	O	ALA	367	21.859	7.269	-1.958	1.00	17.60
ATOM	2913	N	ILE	368	22.151	5.154	-2.719	1.00	17.60
ATOM	2914	CA	ILE	368	23.369	5.440	-3.450	1.00	17.60
ATOM	2915	CB	ILE	368	24.241	4.238	-3.703	1.00	17.60
ATOM	2916	CG2	ILE	368	25.052	4.315	-2.455	1.00	17.60
ATOM	2917	CG1	ILE	368	23.629	2.938	-4.076	1.00	17.60
ATOM	2918	CD1	ILE	368	24.677	2.182	-4.878	1.00	17.60
ATOM	2919	C	ILE	368	23.701	6.060	-4.806	1.00	17.60
ATOM	2920	O	ILE	368	22.151	6.507	-5.228	1.00	17.60
ATOM	2921	N	HIS	369	24.324	6.102	-5.503	1.00	17.60
ATOM	2922	CA	HIS	369	24.369	6.687	-6.795	1.00	17.60
ATOM	2923	CB	HIS	369	23.365	6.052	-7.748	1.00	17.60
ATOM	2924	CG	HIS	369	23.162	6.872	-9.024	1.00	17.60
ATOM	2925	CD2	HIS	369	21.953	7.521	-9.335	1.00	17.60
ATOM	2926	ND1	HIS	369	24.063	7.167	-9.937	1.00	17.60
ATOM	2927	CE1	HIS	369	23.459	7.987	-10.783	1.00	17.60
ATOM	2928	NE2	HIS	369	22.193	8.212	-10.434	1.00	17.60
ATOM	2929	C	HIS	369	24.027	8.162	-6.829	1.00	17.60
ATOM	2930	O	HIS	369	22.930	8.697	-6.651	1.00	17.60
ATOM	2931	N	ASP	370	25.077	8.621	-7.475	1.00	17.60
ATOM	2932	CA	ASP	370	25.319	9.962	-8.033	1.00	17.60
ATOM	2933	CB	ASP	370	25.602	11.006	-6.846	1.00	17.60
ATOM	2934	CG	ASP	370	25.040	10.621	-5.425	1.00	17.60
ATOM	2935	OD1	ASP	370	23.831	10.619	-5.222	1.00	17.60
ATOM	2936	OD2	ASP	370	25.779	10.239	-4.512	1.00	17.60
ATOM	2937	C	ASP	370	26.598	9.434	-8.865	1.00	17.60
ATOM	2938	O	ASP	370	27.703	9.719	-8.502	1.00	17.60
ATOM	2939	OXT	ASP	370	26.366	8.539	-9.720	1.00	17.60
TER									

WO 93/02209 PCT/US92/06137

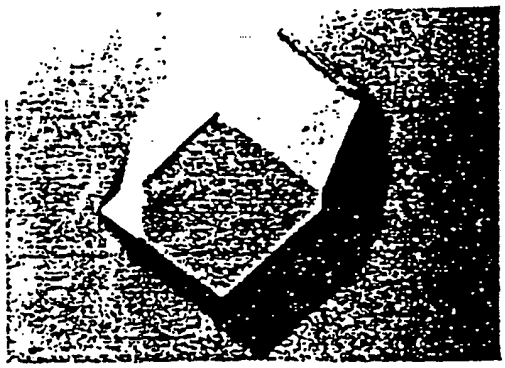

FIGURE 18A

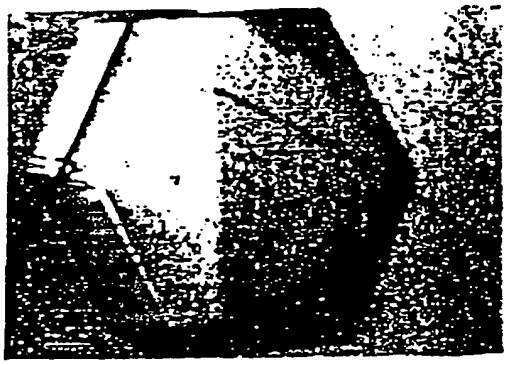

FIGURE 18B

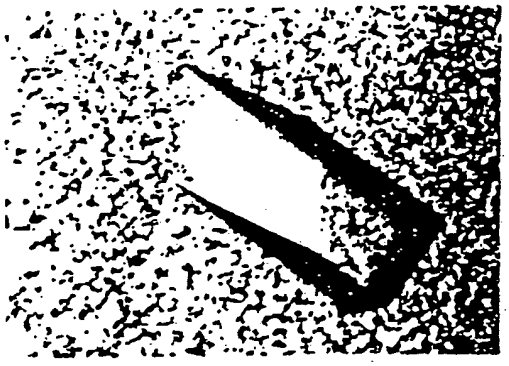

FIGURE 18C

TABLE 1 Structure Solution Statistics

(a). Diffraction Data:

Data Sets	No. of Crystals	d_{min} (Å)	No. of Measurements	No. of Reflections	$\langle I/\sigma(I) \rangle$	Completeness (%)	R_{sym}
Native-1	2	2.7	58889	12713	12.9	98.1	0.061
Native-2	1	2.7	27067	11291	13.2	87.3	0.040
PIMB-1	1	3.0	30973	7233	13.3	76.1	0.063
PIMB-2	1	3.0	23476	8809	6.9	92.1	0.075
MgATP	1	2.7	26464	11840	11.1	91.1	0.048

(b) SIRAS Phasing Statistics:

		Average Shell Resolution (Å)							
	Overall	11.72	7.70	6.11	5.22	4.63	4.20	3.87	3.61
Mean figure of merit	0.57	0.74	0.75	0.68	0.62	0.55	0.53	0.47	0.43
PIMB-1									
acentric r.m.s. f_h/E_{iso}	2.73	3.27	3.80	3.70	3.00	2.54	2.56	2.26	2.05
r.m.s. $\Delta F_{anom}/E_{anom}$	0.96	1.53	1.68	1.41	1.19	1.05	0.89	0.78	0.60
R_c	0.50	0.34	0.38	0.45	0.51	0.78	0.64	0.70	0.81
PIMB-2									
acentric r.m.s. f_h/E_{iso}	2.26	3.89	3.72	3.35	2.81	2.34	2.08	1.83	1.51
R_c	0.60	0.37	0.53	0.58	0.64	0.75	0.71	0.65	0.61

(c) Refinement:

Model	No. of Residues/Chains	Initial R-factor	Final R-factor	B	Data Selection
A. First unrefined partial	275/4	0.473	0.304	overall	10-2.7 Å, F/σ > 2
B. First unrefined full	356/2	0.434	0.228	overall	10-2.7 Å, F/σ > 2
C. Latest X-PLOR	356/2	—	0.195	individual	10-2.7 Å, F/σ > 2
D. TNT	356/2	0.221	0.212	individual	40-2.7 Å

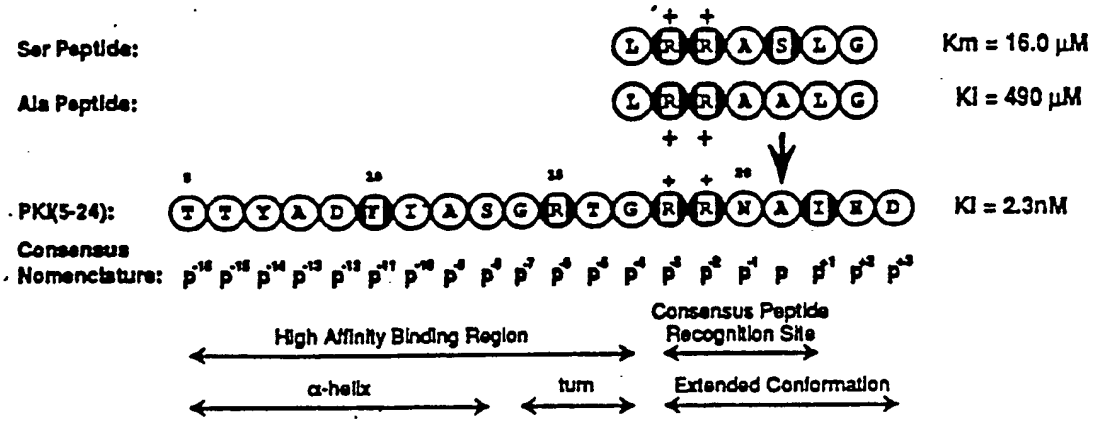
Ser Peptide:
Km = 16.0 μM
Ala Peptide:
KI = 490 μM
PKI(5-24):
KI = 2.3nM
Consensus Nomenclature:
High Affinity Binding Region
Consensus Peptide Recognition Site
α-helix
turn
Extended Conformation

TABLE 2

TABLE 3

POINTS OF CONTACT	POSITION	cAPK	CKII
P+1	197	Thr	Val
	198	Leu	Arg
	199	Cys	Val
	200	Gly	Ala
	201	Thr	Ser
	202	Pro	Arg
	203	Glu	Tyr
	204	Tyr	Phe
	205	Leu	Lys
P-2	170	Glu	His
	230	Glu	Glu
P-3	127	Glu	Asp
	331	Glu	
P-6	203	Leu	
P-11	235	Tyr	
	236	Pro	
	237	Pro	
	238	Phe	
	239	Phe	

TABLE 4

Angstroms apart	Atom 1	Atom 2
5.29	ASP 184 CA	GLY 186 CA
5.73	GLU 91 CA	GLY 186 CA
6.46	ASN 171 CA	ASP 184 CA
7.41	ASN 171 CA	ASP 166 CA
7.61	ASP 166 CA	GLY 186 CA
7.87	ASP 184 CA	GLU 91 CA
8.20	ASP 166 CA	ASP 184 CA
9.20	ASP 184 CA	LYS 72 CA
9.90	GLY 52 CA	LYS 72 CA
10.15	ASN 171 CA	GLY 186 CA
10.29	ASP 184 CA	GLY 52 CA
10.53	GLY 52 CA	GLY 186 CA
10.78	ASN 171 CA	GLY 52 CA
10.91	GLY 186 CA	LYS 72 CA
11.29	GLU 91 CA	LYS 72 CA
11.80	ARG 280 CA	GLU 208 CA
12.27	ASP 166 CA	GLU 91 CA
12.65	ASP 166 CA	GLY 52 CA
13.52	ASN 171 CA	LYS 72 CA
14.07	ASN 171 CA	GLU 91 CA
15.02	GLU 91 CA	GLY 52 CA
15.07	ASP 166 CA	GLU 208 CA
16.54	ASP 166 CA	LYS 72 CA
18.58	ARG 280 CA	ASP 166 CA
19.99	GLU 208 CA	GLY 186 CA
22.00	ASN 171 CA	GLU 208 CA
22.82	ASP 184 CA	GLU 208 CA
23.37	GLU 91 CA	GLU 208 CA
23.49	ARG 280 CA	ASN 171 CA
24.87	ARG 280 CA	GLY 186 CA
25.18	GLU 208 CA	GLY 52 CA
25.61	ARG 280 CA	ASP 184 CA
27.34	ARG 280 CA	GLU 91 CA
30.53	GLU 208 CA	LYS 72 CA
30.83	ARG 280 CA	GLY 52 CA
34.67	ARG 280 CA	LYS 72 CA

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/06137

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C12Q1/00; C12Q1/48; C12N9/99; G01N33/68
C07K13/00; A61K37/64; C07K15/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C12Q ; C12N ; G01N ; A61K C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	WO,A,8 907 654 (PROGENICS PHARMACEUTICALS) 24 August 1989 see claims; example 1 ---	1
A	EP,A,0 359 981 (BOEHRINGER) 28 March 1990 see claims ---	1,29
	-/--	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04 NOVEMBER 1992	16. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DELANGHE L.L.M.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	CHEMICAL ABSTRACTS, vol. 105, no. 21, 24 November 1986, Columbus, Ohio, US; abstract no. 186487d, CLORE, G.MARIUS ET AL. 'Stereochemistry of binding of the tetrapeptide acetyl-Pro-Ala-Pro-Tyr-NH2 to porcine pancreatic elastase.Combined use of two-dimensional transferred nuclear Overhauser enhancement measurements,restrained molecular dynamics,X-ray crystallography and molecular modelling.' page 314 ; see abstract & J.MOL.BIOL. vol. 190, no. 2, 1986, ENG pages 259 - 267 ---	1
P,X	CHEMICAL ABSTRACTS, vol. 115, no. 13, 30 September 1991, Columbus, Ohio, US; abstract no. 130637s, KNIGHTON, DANIEL R. ET AL. 'Crystallization of cAMP-dependent protein kinase.Cocrystals of the catalytic subunit with a 20 amino acid residue peptide inhibitor and magnesium-ATP diffract to 3.0 A resolution.' page 453 ; see abstract & J.MOL.BIOL. vol. 220, no. 2, 1991, ENG pages 217 - 220 ---	1
P,X	SCIENCE vol. 253, no. 5018, 26 July 1991, LANCASTER, PA US pages 414 - 420 D.R.KNIGHTON ET AL. 'Structure of a peptide inhibitor bound to the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase.' see page 420 see the whole document -----	1-66

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9206137 SA 62983

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/11/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8907654	24-08-89	US-A- 4980281	25-12-90
		AU-B- 612948	18-07-91
		AU-A- 3184089	06-09-89
		EP-A- 0403506	27-12-90
		JP-T- 3503598	15-08-91
EP-A-0359981	28-03-90	DE-A- 3827974	22-02-90
		AU-B- 627207	20-08-92
		AU-A- 3955089	22-02-90
		JP-A- 2108636	20-04-90